Soil Transmitted Helminth Infections: The Nature, Causes and Burden of the Condition

DISEASE CONTROL PRIORITIES PROJECT

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DISEASE CONTROL PRIORITIES PROJECT

BACKGROUND

In the late 1980s, the World Bank initiated work to inform priorities for control of specific diseases and to generate comparative cost-effectiveness estimates for interventions addressing the full range of conditions important in developing countries. The purpose of the comparative cost-effectiveness work was to provide one input into decision-making within the health sectors of highly resource-constrained countries. This process resulted in the 1993 publication of *Disease Control Priorities in Developing Countries**. A decade after publication of the first edition, the World Bank, the World Health Organization, and the Fogarty International Center (FIC) of the U.S. National Institutes of Health (NIH) have initiated a "Disease Control Priorities Project" (DCPP) that will, among other outcomes, result in a second edition of *Disease Control Priorities* in Developing Countries (DCP*2*). The DCPP is financed in part by a grant from the Bill & Melinda Gates Foundation. DCP*2* is intended both to update DCP*1* and to go beyond it in a number of important ways, e.g. in documentation of success stories, in discussion of institutional and implementation issues, and in explicit discussion of research and development priorities. Publication of DCP*2* is intended for mid-2005.

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Abstract

More than one dozen different species of soil-transmitted helminths infect humans, especially in the tropical and subtropical parts of the developing world. However, four nematodes in particular stand out because of their widespread prevalence and distribution that result in hundreds of millions of human infections. These include the large roundworm, *Ascaris lumbricoides*, the whipworm *Trichuris trichiura*, and two species of hookworm, *Necator americanus* and *Ancylostoma duodenale*. The WHO estimates that almost 2 billion people are infected with one or more of these soil-transmitted helminths, accounting for up to 40% of the global morbidity from infectious diseases, exclusive of malaria. The greatest numbers of soil-transmitted helminth infections occur in tropical and subtropical regions of Asia, especially China, India and Southeast Asia, as well as Subsaharan Africa. Of the 1-2 billion soil-transmitted helminth infections worldwide, approximately 300 million infections result in severe morbidity, which are associated with the heaviest worm burdens. Susceptibility to heavy infections has genetic, immunological and behavioral components. However, the greatest single predictor of heavy worm burdens is age. Epidemiologic studies conducted throughout the developing world point to school-aged children as the population at greatest risk for acquiring heavy infections with Ascaris and Trichuris infections. These children suffer the consequences of acute Ascaris intestinal obstruction, hepatobiliary ascarisiasis, Trichuris dysentery syndrome, or rectal prolapse. However, even more significant are the physical growth retardation, cognitive and educational impairments caused by heavy chronic infection, which have led to calls for school-based periodic anthelminthic drug deworming programs. Although children are also at risk for heavy hookworm infections, in many regions, the highest hookworm burdens occur in adults. Two populations at special risk are pregnant women and the elderly. New studies measuring population attributable risks identify hookworms as significant causes of iron-deficiency anemia in all three groups. Additional data suggests that hookworms may be directly immunosuppressive and could promote increased susceptibility to intercurrent viral and other infections, possibly including HIV-AIDS and malaria. Therefore, current DALY measurements may underestimate the true global burden of disease caused by soil-transmitted helminths.

Soil Transmitted Helminth Infections: The Nature, Causes And Burden Of The Condition

Peter J. Hotez M.D., Ph.D., Nilanthi de Silva Ph.D., Simon Brooker Ph.D.
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1. Causes and characteristics

Ascaris and Trichuris Infections

An estimated 1.05 and 1.3 billion persons harbor the whipworm *Trichuris trichiura* and the roundworm *Ascaris lumbricoides*, respectively (Chan et al, 1994; de Silva et al, 1997; Stephenson et al, 2000). Among children, an estimated 59 million cases of Ascaris infection are associated with significant morbidity; the estimate for acute illness is 12 million cases per year with approximately 10,000 deaths (de Silva et al, 1997). Both parasites have a widespread distribution in the tropics and subtropics, including both rural areas as well as the slums of large urban areas of the developing world. The Chinese national survey conducted between 1988 and 1992 estimated that 531million of Ascaris infection and 212 million cases of Trichuris infection occur in that country alone (Hotez et al, 1997). Of the two, Ascaris is typically the more predominant soil-transmitted helminth in any given area, although Trichuris predominates in some parts of Southeast Asia, Africa, and the Caribbean. In some regions the prevalence may reach 95% among children (Stephenson et al, 2000). In developing countries, it is common to encounter children who are co-infected with both Ascaris and Trichuris, and there is a statistically significant association between the two (Howard et al, 2002). Ascaris and Trichuris infections are not exclusively tropical and still occur in poor, underserved areas of the industrialized nations, including the United States (Blumenthal and Schultz, 1975; Jones, 1983; Kappus et al, 1994) and the United Kingdom (Crompton, 1989b)

Etiology

T. trichiura is a member of the nematode superfamily Trichuroidea, and therefore related to the pathogen *Trichinella spiralis* (Cooper, 1995). No other members of the genus are significant pathogens for humans. However, a related species, *Trichuris suis* may occasionally infect humans as a zoonosis transmitted from porcine reservoir hosts (Beer, 1976). The adult worm is approximately 4 cm long; its whip-like shape refers to the wider posterior section containing the parasite's reproductive organs and intestine, whereas its long, finely attenuated anterior end contains the stichosome, a long pharynx lined with stichocyte secretory cells (Cooper, 1995). Eggs passed in the feces of an infected individual have a classic barrel shape with a plug at each pole. After embryonation in the soil, a process that requires 2-4 weeks, a larva develops. Human transmission occurs by ingestion of the embryonated eggs, which release larvae that molt and burrow into the colonic epithelia upon arrival into the large intestine.

Ascaris was probably the first etiologic agent of infection ever described in humans with descriptions of the parasite going back to ancient times, and the first scientific description dating back to 1683 (Crompton, 1989a). The human parasite is a member of the family Ascarididae, and closely related to the swine parasite *Ascaris suum*. The adult stage of *A. lumbricoides* is a cylindrical pink or cream coloured worm of the family Ascarididae and the superfamily Ascaridoidea. The male is smaller (120 – 250 mm by 3 – 4 mm) than the female (200 – 400 mm by 5 – 6 mm). The adult worm preferentially resides in the jejunum where it orients with the head facing the direction of the intestinal flow (Makidono, 1956). Mature female *A. lumbricoides* worms produce 100,000 – 200,000 fertilised or unfertilised eggs per day. The detection of *Ascaris* eggs in fresh or fixed stool samples examined by bright field microscopy remains the most reliable means of identifying cases of ascariasis for both individual patients and community surveys. Eggs excreted in faeces require a period of maturation in soil. Under advantageous conditions, of warm, moist shaded soils, the embryo moults within the eggshell. The infective stage is a second stage larva within the egg. The period of development in the soil is temperature dependent and may range from 2 weeks to several months. Eggs are infectious by ingestion. Larvae do not hatch in soil and do not invade the skin. The larvae that emerge from ingested eggs in the jejunum penetrate the intestinal wall and migrate by way of the hepatic venules to the right side of the heart and the pulmonary circulaion, where they break into to alveolar spaces and undergo two further moults. From the alveoli, the 1.5mm long larvae ascend to the trachea, and are swallowed, undergo a last moult in the intestine, and develop to adults. From ingestion of infective eggs to the production of eggs by mature adult worms, development takes about 10 –12 weeks. The adult worm has a life span of about a year. Because its large size allows for dissection and recovery of individual nematode organs and cuticle, and because of the relative abundance of adult *A. suum* worms available from abattoirs, there is probably more biochemical information about Ascaris available in the literature than for almost any other invertebrate. This includes detailed studies of Ascaris metabolism and physiological responses to the anaerobic environment in the gut (Kita and Takamiya, 2002), Ascaris reproduction (Bottino et al, 2002), and Ascaris genetics (Muller and Tobler, 2000).

Several investigations have been conducted in order to determine whether *A. lumbricoides* and *A. suum* are truly separate species and if so, whether cross-transmission between humans and pigs occur. This is not simply an academic question since in many parts of the world where people raise pigs, especially South America, China, and Southeast Asia, it is important to know whether zoonotic transmission accounts for a significant number of human cases. Over the last decade molecular tools including mitochondrial DNA sequencing and restriction site polymorphisms in the introns of Ascaris nuclear genes have been employed to resolve the issue (Anderson et al, 1993; Anderson, 1995; Anderson and Jaenike, 1997; Peng et al, 1998; Crompton, 2001). So far, it appears that Ascaris in humans and pigs in Central America and China comprise reproductively isolated populations, suggesting that zoonotic transmission leading to patent infections is not a frequent occurrence (Peng et al, 1998). However, visceral larva migrans from *Ascaris suum* infections has been described from Japan, and presumably elsewhere (Sakakibara et al, 2002).

Burden of disease

For all human soil-transmitted helminths studied to date, which so far includes Ascaris, Trichuris, both hookworms, Enterobius, and Ternidens, worm burdens exhibit a highly overdispersed distribution so that most individuals harbor just a few worms in their intestines while a few hosts harbor disproportionately large worm burdens (Bundy, 1995). As a general rule, approximately 70% of the worm population is harbored by 15% of the host population. These heavily infected individuals are simultaneously at highest risk of disease and the major source of environmental contamination (Bundy, 1995). In the case of Ascaris and Trichuris infections, overdispersed distributions also exhibit age dependency, with a peak in the child age class, but with a subsequent decline among adults (Bundy et al, 1988; Bundy, 1995). Maximum prevalence of both Ascaris and Trichuris infections is usually attained before 5 years of age (Bundy, 1995).

There is a relationship between prevalence and intensity (worm burdens) of Ascaris and Trichuris infections, although this is not always linear. The most accurate means to obtain intensity data is to treat a given population with anthelminthics and then to collect and enumerate the expelled worms. This can provide up to a 90% accurate estimate of worm burden (Bundy, 1995). Studies indicate that with low and moderate worm burdens, the community prevalence provides a reasonable estimate of mean intensity, but that this relationship breaks down with heavy infections (Bundy, 1995). Therefore in areas of high transmission areas, it is usually necessary to directly determine intensity. Numerous studies covering a diversity of geographic regions worldwide indicate that for Ascaris and Trichuris infections maximum worm burdens occur in human populations at 5-10 years of age (Bundy, 1995). Further evidence implicates strength of association between Ascaris and Trichuris in which infection with one increases the likelihood of concurrent infection with the other (Howard et al, 2002).

Because most the significant physical and intellectual growth disturbances from these two parasites occur as a consequence of moderate and heavy worm burdens, the age associated epidemiology of Ascaris and Trichuris has focused international attention on the plight of infected school-aged children in developing countries. However, the actual threshold at which Ascaris and Trichuris worm burdens result in childhood morbidity is still controversial. Bundy (1995) points out the difficulties of assigning a relationship between infection intensity and clinical signs, because of 1) the non-linear relationship between intensity and pathogenesis and, 2) the difficulties of measuring and attributing morbidity in underserved populations suffering from multiple other underlying conditions including malaria, other helminths (e.g., schistosomiasis, hookworm), and malnutrition. In some cases the effects specifically linked to Ascaris and Trichuris can only be sorted out by following children longitudinally after specific anthelminthic therapy or through modern analytical procedures (Guyatt et al, 1990; Guyatt and Bundy, 1991). Variance decomposition methods have also been useful for this purpose (Bethony et al, 2002).

Specific aspects of Trichuris infection

Trichuris causes host injury both through direct effects by invading the colonic mucosa and through the systemic effects of infection. The cecum is the preferential site for invasion although heavy infections will extend throughout the colon and even distally to the rectum (Hotez, 2000). The adult parasite leads both an intracellular and an extracellular existence in which the attenuated anterior end becomes embedded in epithelial tunnels it creates by secreting novel pore forming proteins (Drake et al, 1994), while the larger posterior end extrudes into the lumen. Inflammation at the site of attachment results both from disruption of the normal colonic architecture as well as host inflammation comprised of macrophages and proinflammatory cytokines in the lamina propria (MacDonald et al, 1994). Several investigators have pointed out the clinical similarities between the pediatric colitis caused by Trichuris infection and more established causes of inflammatory bowel disease such as Crohn's disease and ulcerative colitis. These clinical features include impaired growth, anemia of chronic disease, and even finger clubbing (Cooper, 1995; Hotez, 2000)

The most severe manifestation of heavy infection among children is the Trichuris dysentery syndrome (TDS), which is associated with chronic dysentery, rectal prolapse, anemia, and growth stunting (Cooper and Bundy, 1988; Cooper, 1995; Stephenson et al, 2000). Growth stunting is sometimes reversible with specific anthelminthic treatment and supplemental oral iron. Intellectual and cognitive impairments and delays are also associated with chronic heavy infections (Sternberg et al, 1997; Drake et al, 2000). These deficits sometimes reverse following anthelminthic therapy, particularly when treatments are linked to psychological support (Stephenson et al, 2000). The mechanisms by which Trichuris causes neuropsychiatric deficits in childhood are unknown, but their adverse impact on educational achievements and downstream success in adult life are potentially profound. They also add significantly to the burden of disease caused by Trichuris, although assigning quantitative values to this feature is difficult.

While there is general agreement on the profound impact of TDS on childhood physical and mental health, the condition occurs only among the roughly 15% of Trichuris infected children with the heaviest worm burdens. The threshold at which moderate or even light infections might exert an impact on childhood growth and development is less certain. For instance, using rates of alpha-1-antitrypsin clearance as a measure of intraluminal gut leakage, Cooper et al (1992) determined that significant effects occur with worm burdens of just a few hundred or less. Even more subtle consequences might be measured in studies that examine childhood cognition (Bundy, 1995; Drake et al, 2000). A double-blind placebo trial with anthelminthics demonstrated significant improvement in cognitive abilities among moderately infected schoolchildren (Nokes et al, 1991a,b). Overall, the health consequences of Trichuris infection in a given community are vastly underreported (Cooper et al, 1986).

Specific aspects of Ascaris infection

Ascaris infections are classified by their clinical expression into four different groups as shown in Table 1 (de Siliva et al, 1997).

During early infections, the invasive larval stages of *Ascaris* will elicit a host eosinophilic inflammatory response in the liver (hepatitis) and lung (Loeffler's pneumonitis), which clinically may resemble visceral larval migrans caused by Toxocara. The phase of larval migration is known to be associated with a distinctive type of pneumonitis known as Loeffler's Syndrome. This syndrome is characterized by varying pulmonary infiltrates, mild to marked respiratory symptoms and peripheral eosinophilia (Loeffler, 1956). It appears that Loeffler's Syndrome occurs with seasonal ascariasis transmission as in Saudi Arabia (Gelpi & Mustafa 1967), rather than with continued transmission throughout the year (Spillman 1975).

Adult and larval *Ascaris* release extremely potent, volatile allergens (Coles, 1985, Kennedy, 1992). These may initiate the asthma-like symptoms sometimes associated with ascariasis. However, the relationship between *Ascaris*, allergy and asthma is still unclear. Regular anthelmintic treatment have been shown to improve the clinical symptoms of asthma in asthmatics living in an area endemic for soil-transmitted helminth infections (Lynch et al 1997). Venezuelan children with a strong atopic background have been found to have IgE responses concordant with an enhanced protective response to Ascaris, with significantly lower intensities of infection than non-atopic controls (Lynch et al 1998). Continuous exposure to *Ascaris* infection may in some way, reduce the development of asthma as appears to be the case with Loeffler's syndrome. In a study of asthmatic and healthy pre-school children in Tanzania, where the overall prevalence of ascariasis was around 40%, the investigators found no evidence for *A. lumbricoides* as a cause of asthma (Carswell et al, 1977). Several studies have also examined the role of the related canine ascarid, *Toxocara canis*, as a possible environmental cause of asthma in Europe (Buijs et al, 1994). Because of the high rate of toxocariasis among Hispanic children living in urban centers in the United States, *T. canis* has been investigated as an emerging etiologic agent of asthma (Sharghi et al, 2001).

The most severe manifestations of Ascaris occur as a consequence of either physical obstruction in the intestinal tract by a bolus of adult worms or because of adult parasite migrations into the biliary tree. Ascaris obstruction may account for up to 35% of all intestinal obstructions in the developing world (O'Hanley and Pool, 1995). Among the factors associated with acute obstruction are high fever, acute diarrhea, peppery foods, inhalant anesthesia, and other physiological stresses (O'Hanley and Pool, 1995). This phenomenon accounts for most of the 10,000 deaths annually from ascariasis and, together with heptaobiliary and pancreatic ascariasis (HPA), the roughly 0.05 to 1 hospitalized cases per 1000 Ascaris infections (Crompton, 1989b). Among adults screened by ultrasonography from a general population in Kasmir, India, it was determined that 0.5% are affected by HPA (Khuroo et al, 1989; Khuroo, 2001). Because of the higher worm burdens in children, the frequency of

HPA is presumably higher. It is likely that HPA is a reversible condition when *Ascaris* adult worms return to the intestine, frequently after a day or two of colic. However, reinvasion is a common phenomenon, occurring in 15% of patients over a four-year period (Khuroo et al, 1990).

Of greater global health impact than acute obstructive ascariasis or HPA, are the nutritional consequences of chronic ascariasis, including increased fecal nitrogen loss, reduction in the ability to digest lactose, and diminished vitamin A utilization (Nesheim, 1989. Evidence from animal studies demonstrates that Ascaris infection causes a reduction in growth rate, reduces food consumption, interferes with absorption of fat and protein, and produces intestinal damage resulting in reduction of mucosal lactase deficiency (Crompton & Nesheim 2002).

The results of 10 longitudinal studies comparing the growth of Asian and African children infected with *A. lumbricoides* with those given anthelmintics treatment have been reviewed recently (O'Lorcain & Holland, 2000). These 10 studies involved observation periods ranging from 7 weeks to 24 months. Eight of 9 studies using weight in kg for hypothesis testing found a statistically significant improvement in weight after treatment. Seven studies also calculated percentage weight-for-age and all but two showed statistically significant improvements in intervention groups compared to non-intervention groups. Treated children also had a greater increment in height than untreated children in 3 of 6 studies in which height was measured and a greater increment in height-for-age in 3 of 5 studies. The effects on growth are most pronounced in children with the heaviest infections, but light infections may contribute to growth deficits if the nutritional status of the community is poor. There is now general agreement that under certain conditions, infection with *A. lumbricoides* is associated with impaired growth and poor nutritional status in children (Crompton & Nesheim, 2002). Some of these mechanisms linked to malnutrition undoubtedly account for some of the growth impairments seen in children with chronic Ascaris infections. However, it remains difficult to sort out the true contribution of Ascaris infection versus co-infection with other helminths such as Trichuris, and there so far remains no unifying hypothesis to explain how *Ascaris*, Trichuris and hookworm each cause impaired physical growth. It may well be that Ascaris exerts its growth impairment effects via subtle changes in host nutritional status, Trichuris on the basis of inflammatory cytokines, and hookworm through iron deficiency and plasma protein loss.

Improvement of appetite after treatment for ascariasis has been demonstrated most definitively among Indonesian schoolchildren (Hadju et al 1996). A related study, also in Indonesian schoolboys, found increased free play activity in addition to improved appetite and growth rate after treatment for ascariasis and trichuriasis (Hadju et al 1998).

Jejunal biopsies of Ascaris infected children have shown abnormalities including shortened villi, elongated crypts, a decrease in the villus to crypt ratio and cellular infiltration of the lamina propria (Tripathy et al 1972). There is evidence that *Ascaris* infections may significantly reduce lactose tolerance in preschool children (Taren et al 1987, Carrera et al 1984).

Several clinical studies have shown that absorption of Vitamin A is lower in *Ascaris* infected children (Mahalanabis et al 1979, Reddy et al 1986) and infected children have been observed to have a greater incidence of xerophthalmia than controls (Bhattacharyya 1982). Impairment of Vitamin A absorption may be related to the effects of infection on fat absorption.

It is to be expected that children experiencing abdominal pain, nausea and digestive disturbances due to helminth infection will probably have a reduced attention span when present in school, and may even miss a significant amount of schooling due to chronic illness. However, demonstration of any such adverse effects of intestinal nematode infection on the intellectual development and cognitive performance of children is far from straightforward and beset by numerous confounding variables (Crompton 2001). A few studies have implicated *Ascaris* infections in impairment of mental processing in some children. For example, a study conducted among Indonesian schoolchildren (among whom the prevalence of ascariasis was 58%) found that cognitive test results indicated significant improvements in learning ability, concentration and eye-hand coordination 5 months after treatment with mebendazole (Hadidjaja et al 1998).

Studies on the relationship between prevalence and disease suggest that disease increases dramatically with increased prevalence (Guyatt and Bundy, 1991). However, the parameters required to establish the exact threshold of disease are still not defined. The concentration of eggs in faeces (as estimated, for example, by the Kato-Katz technique) is commonly used as an indirect estimate of the worm burden. However, this involves many assumptions as well as potential sources of inaccuracy. First, only female worms produce eggs, so an even sex ratio is assumed. In addition, the concentration of eggs can vary within a faecal sample and from day to day. It also appears that the fecundity of female *A. lumbricoides* might vary around the world (Hall & Holland 2000). The investigators suggest that, for example, an egg count of 50 000 eggs per gram (epg) faeces would be reached in Mexico with a burden of 25 worms; in Myanmar, Madagascar and Nigeria at around 100 worms; in Iran at about 260 worms; but not within a biologically possible worm burden in Bangladesh. Based on this, the use of a threshold of 50 000 epg faeces to define a heavy infection with *A. lumbricoides* and to decide on the frequency with which mass treatment should be applied has been questioned.

It has been suggested that ascariasis may modulate the immune response to other infections. For example, infection with *A. lumbricoides* alone or in conjuction with *Necator americanus* was found to be associated with a protective adjusted odds ratio when cases of cerebral malaria were compared with mild controls (Nacher et al 2000, 2002a). However, in a prospective study on Thai villagers, the same investigators found that helminth-infected subjects were more likely to develop falciparum malaria (Nacher et al 2002b). Infection with A. lumbricoides has also been found to diminish the magnitude of the vibriocidal antibody response as well as the cytokine response to a live oral cholera vaccine (Cooper et al 2000, 2001).

Hookworm

Human hookworm infection is a soil-transmitted intestinal helminthiasis caused by either *Necator americanus* or *Ancylostoma duodenale*. Intestinal infections with the canine hookworms *Ancylostoma ceylanicum* and *Ancylostoma caninum* rarely occur as a consequence of zoonotic transmission (Prociv and Croese, 1996). Like Ascaris and Trichurs, hookworms are among the most ubiquitous infectious agents of humankind; some estimates suggest that as many 1.2 billion people are infected worldwide (Chan et al, 1994). The infection is found wherever rural poverty occurs in a tropical or subtropical climate and adequate moisture. In the Western Hemisphere hookworm is common in rural areas of Central America and tropical regions of South America, including Brazil and Venezuela. In Asia, hookworm is highly endemic in South China, Southeast Asia, and the Indian Subcontinent. Hookworm is common throughout Subsaharan Africa and in some regions of Egypt. Because of its virulence and worldwide prevalence, Prof. Norman Stoll of the Rockefeller Institute and Foundation labeled hookworm as “The Great Infection of Mankind” (Stoll, 1962).

Etiology

Hookworms are nematodes belonging to the family Ancylostomatidae, a part of the superfamily Strongyloidea. The two major genera that affect humans, Necator and Ancylostoma are characterized by the presence of oral cutting organs in the adult stages (Hotez, 1995). *Necator americanus* is considered by some to be the only member of its genus, although a second species from badgers, *N. miyazakinensis* has also been described from Japan (Komiya and Yasuraoka, 1966). The major representative of the genus Ancylostoma to infect and complete development in humans is *Ancylostoma duodenale*. In contrast to the major human (anthropophilic) species, *A. ceylanicum*, a parasite of dogs and cats is also infective to humans in some regions of Asia, but it is not considered a major pathogen (Hotez, 1995), while the classic dog hookworm *A. caninum* has been linked to an eosinophilic enteritis syndrome in Queensland Australia (Prociv and Croese, 1996). Yet another canine and feline hookworm, *A. braziliense* causes cutaneous larva migrans.

There are significant pathobiological differences between the two major human hookworms (Hoagland and Schad, 1978; Hotez, 1995). Unlike *N. americanus*, which can complete its life cycle in humans only after skin penetration, A. duodenale is also transmitted by oral ingestion of the larvae. *N. americanus* is smaller than *A. duodenale* and produces fewer eggs, and causes less blood loss (Albonico et al, 1998). *N. americanus* is considered by some to be better adapted to human parasitism because of its diminished virulence relative to *A. duodenale* (Hoagland and Schad, 1978). Necator may be more adept at immune evasion (Pritchard and Brown, 2001; Hotez et al, 2003). In contrast, *A. duodenale* is considered to be the more “opportunistic species” because of its ability to survive in more extreme environmental conditions, its oral infectivity, greater fecundity and higher virulence (greater blood loss) (Hoagland and Schad, 1978). This last feature accounts for the observation, best documented in Tanzania, that the species of hookworm being transmitted in a community strongly influences the burden of iron deficiency anaemia in the community (Albonico et al, 1998).

Unlike, *N. americanus, A. duodenale* also has the unique ability to undergo arrested development in humans and may, under certain conditions (Schad et al, 1973; Schad, 1990), enter human mammary glands during pregnancy prior to lactogenic transmission (Hotez, 1989; Yu et al, 1995).

Burden of disease

Hookworms injure their human host by causing intestinal blood loss leading to iron deficiency and protein malnutrition (Hotez and Pritchard, 1995; Stoltzfus et al, 1997a and b). The parasite induces blood loss directly through mechanical rupture of host capillaries and arterioles followed by the release of a battery of pharmacologically active polypeptides including anticoagulants, antiplatelet agents, and antioxidants (Cappello et al, 1995, 1996; Stanssens et al, 1996; Pritchard, 1996; Furmidge et al, 1996; Zhan et al, 2002; Basavaraju et al, 2002). Hookworms subsequently digest host hemoglobin by employing a carefully orchestrated cascade of hemoglobinases that align the brush border membrane of the parasite's alimentary canal (Loukas et al, 2000; Hotez and Jones, 2002; Williamson et al, 2002 a,b,c; Hotez et al, 2003). Studies of the anemia associated with hookworm blood loss indicate that there is a disproportionate reduction in plasma hemoglobin concentration after some threshold worm burden is exceeded (Bundy, 1995). Although the threshold might be expected to be well established because of the accurate estimates of blood loss caused by each hookworm species (Martinez-Torres et al, 1967), the precise value is actually community dependent because the onset of anemia is dependent on the iron-status and reserves of the host (Lwambo et al, 1991). This in turn depends on a number of factors including dietary iron intake and overall level of nutrition.

Because hookworm-induced blood loss and the resulting iron and protein deficiencies are typically insidious and chronic and do not usually result in death, until recently hookworms were often overlooked as significant causes of morbidity. For instance, hookworms were not placed on the World Health Organization's (WHO) priority list for its Tropical Disease Research (TDR) program during the 1980s (Hotez et al, 2003). Public health interest in hookworm was renewed in the 1990s when new quantitative estimates of disease burden based on disability adjusted life years (DALYs) revealed its global impact (Murray and Lopez, 1996). These data revealed that soil-transmitted helminthiases, which include hookworm, ascariasis and trichuriasis are the most significant parasitic infections of humans with the exception of malaria. The disease burden caused by hookworm alone exceeds three tropical infectious diseases under investigation in the WHO-TDR program, namely African trypanosomiasis, Chagas disease, and leprosy. Hookworm outranks dengue fever. However, even these DALY measurements probably underestimate the true disease burden impact of hookworm. Iron-deficiency anemia is one of the leading causes of morbidity in the developing world, possibly exceeding the impact of HIV/AIDS. New data on the epidemiology of iron deficiency anemia in East Africa and elsewhere points to the important contribution of hookworms to this condition (Stoltzfus et al, 1997 a and b; Dreyfuss et al, 2000).

The clinical effects of hookworm-induced protein loss and iron deficiency secondary to hookworm anaemia are well described in the literature. Some investigators believe that hookworm anaemia is highly focal, and in some instances more common in coastal regions (Lwambo et al, 1991). In addition, hookworm associated Iron deficiency during childhood is partly responsible for its physical and mental growth retardation effects (Hotez, 1989; Sakti et al, 1999; Beasley et al, 2000; Lwambo et al, 2000; Hotez, 2000, Stoltzfus et al, 2001). The growth stunting effects of hookworm were well documented by the early part of the 20th Century (Smillie and Augustine, 1926), as were some of the effects of hookworm on intelligence quotient (Hotez, 1989). However, it is only within the last few years that hookworm-induced iron deficiency was understood to also exert more subtle, yet profound, adverse effects on childhood memory, reasoning ability and reading comprehension (Sakti et al, 1999).

Although the adult hookworms elicit most of the pathology attributed to hookworm, the infective larval stages also release macromolecules upon host entry that contribute to morbidity. These include hookworm derived allergens (Hawdon et al, 1999; Zhan et al, 1999) and tissue invasive enzymes (Hotez et al, 2002; Brown et al, 1999; Zhan et al, 2002). Some of these molecules contribute to the pathogenesis of dermatitis (“ground itch”) and hookworm pneumonitis.

New evidence indicates that chronic hookworm infection leads to a state of immunological hyporesponsiveness possibly linked to diminished host lymphoproliferative responses to hookworm antigens (J. Bethony, M.E. Bottazzi, personal communication). By intracellular cytokine staining, high levels of IL-10 but absent IL-4 were detected in leukocytes from infected patients. These features of hookworm are distinct from other soil-transmitted helminth infections, as well as schistosomiasis, and may account for the high rates of hookworm among middle aged and elderly patients in endemic areas (see below). Immunological hyporesponsiveness induced by hookworms infected individuals could promote susceptibility to intercurrent viral, bacterial or protozoan infections such as measles (Kofoid and Tucker, 1921), HIV-AIDS (Borkow et al, 2000; Wolday et al, 2002) and tuberculosis (Borkow and Bentwich, 2000; Borkow et al, 2001). An association between soil-transmitted helminth infections and increased incidence of *Plasmodium falciparum* malaria has been noted in Thailand (Nacher et al, 2002) and in Nigeria (Egwunyenga et al, 2001), although no studies were done to determine the relative contribution of hookworm to this phenomenon relative to Ascaris and Trichuris. Solid epidemiological evidence for these associations in Subsaharan Africa and elsewhere would dramatically increase our current global burden impact measurements for hookworm.

2. **Risk factors**

Environmental Risk Factors

Urban versus Rural Environments

Ascaris and Trichurs commonly occur both in urban environments, especially urban slums, and in rural areas. In some instances the prevalence of Ascaris infection is actually greater in urban environments (Phiri et al, 2000). In contrast, high rates of hookworm infection are typically restricted to areas where rural poverty predominates (Albonico et al, 1997).

The urban-rural dichotomy between Ascaris-Trichuris versus hookworm can be partly understood by fundamental differences in the life cycles of these soil-transmitted helminths. The infective stages of Ascaris-Trichuris are embryonated eggs having enormous capacity for withstanding the environmental extremes of urban environments. Contained within the inner layer of Ascaris eggs is an unsaponifiable lipid known as ascaroside, which confers many of its hardy properties (Perry and Clark, 1982). Viable Ascaris eggs have been recovered from soil samples for more than 10 years after having been first deposited (Crompton, 1989a). In addition to ascaroside, Ascaris eggs are coated with a mucopolysacccharide that renders them adhesive to a wide variety of environmental surfaces; this feature accounts for their adhesiveness to everything from door handles, dust, fruits and vegetables, paper money and coins, etc. (Kagei, 1983; Crompton, 1989a). The "five f's" of parasitology, fingers, feces, fomites, flies and food might have originated with Ascaris in mind. Transmission through the ingestion of Ascaris eggs adhering to vegetables is a major route of transmission (Raisanen, 1985).

The social and environmental conditions in the unplanned slums of developing countries are ideal for the persistence of *A. lumbricoides* and *T. trichiura*. Many surveys have shown a high prevalence of these infections in children of slums, shanty towns and squatter settlements (Crompton & Savioli, 1993). However, the population density in urban slums should facilitate drug delivery and opportunities for health education. Individuals should also have easier access to purchasing anthelmintic drugs for treatment of their families (Crompton 2001).

Soil

Ascaris eggs develop best in less permeable clay soils, with survivability increasing with their soil depth (Crompton, 1989a). Clay soils are believed to prevent egg dispersal by water (Mizgajska, 1993). The vulnerability of Ascaris eggs to direct sunlight may account for part of this observation. Unlike Ascaris and Trichuris eggs, hookworm eggs hatch in the soil and give rise to first-stage larvae, which molt to infective larval stages only under precise conditions. Egg development in the soil is dependent upon a number of factors including temperature (optimal development at 20-30 C), and adequate shade and moisture (Komiya and Yasuraoka, 1966). Mathematical models based on laboratory data show that *A. duodenale* eggs hatch sooner than N. americanus eggs, but at a marginally slower rate (Smith and Schad, 1989). Well-aerated, non-adhesive sandy soils (0.5 mm to 2 mm) are particularly conducive to promoting hookworm egg hatching, larval development, and larval migration (Beaver, 1975). The additional presence of silt that contains microscopic and barely visible particles that provides optimal conditions. Such soil is sometimes known as 'sandy loam' (Beaver, 1975). Changing environmental conditions, specifically deforestation and subsequent silting of local rivers may cause deposition of sandy loam topsoils and increased soil moisture that might promote the emergence of endemic hookworm (Lilley et al, 1997).

Climate

Adequate warmth and moisture are key features for each of the soil-transmitted helminths. Ascaris and Trichuris eggs are hardier than hookworm L3 and therefore survive drier climates better. However, even for Ascaris and Trichuris, the rates of infection are low in arid climates. At low humidity (atmospheric saturation less than 80%), human Ascaris ova do not embryonate; there appears to be no upper lethal limit on relative humidity (Brooker & Michael, 2000). This probably accounts for the low rates of infection in Chad and Mali, where tropical conditions in combination with poverty would ordinarily result in high endemicity (Crompton, 1989b). For hookworm, moisture is especially critical. The infective third-stage larvae (L3) migrate along films of moisture. The presence of moisture will therefore allow L3 to travel vertically in the soil, particularly at night.

Since the presence vegetation tends to prevent evaporation and conserve soil moisture, this feature has been used as a useful proxy measure of soil moisture. Around vegetation, L3 will migrate to a height of 30-40 cm in 24-48 hr (Komiya and Yasuroaka, 1966), if the film of moisture extends this far. L3 are susceptible to dessication and will migrate up and down vertically in response to changing moisture conditions, until the lipid reserves of these non-feeding stages are exhausted (Hotez, 1995).

It has been suggested that total rainfall in an area and its seasonal distribution may also help explain observed patterns of infection: wetter areas are usually associated with increased transmission of all three major soil transmitted helminth infections (Brooker & Michael, 2000). A study of the prevalence of helminth infections along the coastal plains of South Africa found transmission of *A. lumbricoides* to correlate with variables based on annual data, particularly rainfall and temperature (Appleton et al 1999). Studies from West Africa suggest that a minimum of 1400 mm annual rainfall is necessary for the prevalence of *A. lumbricoides* to exceed 10% (Prost 1987, Brooker & Michael, 2000). However, recent work in Uganda demonstrates that moderate to high prevalences can occur in areas with an annual rainfall between 800 – 1400 mm (Kabatereine & Brooker, unpublished). This difference illustrates how relationships between prevalence of infection and ecological variables may be local, so it will be important to investigate such relationships in different ecological zones.

Altitude probably affects soil helminth transmission through the associated changes in temperature and humidity. Survey results in South Africa found that Ascaris occurred at altitudes up to about 1700m in the foothills of the Drakensberg Mountains, although at decreasing prevalences (Appleton & Gouws, 1996). In Ethiopia, prevalence rates of about 30% ascariasis have been described at altitudes above 2500 m (Jemaneh 1998). Prevalence rates of 11 – 15% have been described from the North Bolivian Altiplano, at altitudes of 3800 – 4200m (Flores et al 2001).

Use of Geographical Information Systems (GIS) and satellite sensor data (Remote Sensing, RS) can lead to a better understanding of the thermal limits of infection (Brooker & Michael 2000). For example, observations in Cameroon, Chad and Uganda suggest that *A. lumbricoides* and *T. trichiura* do not occur in areas where land surface temperature (LST) exceeds 37°C (Brooker et al., 2002a, 2002b; Kabatereine & Brooker, unpublished). Such thermal limits are also supported by available experimental data: the optimal temperature for the embryonation of Ascaris spp. has been reported to be 31º C (Seamster, 1950), and 38º C is lethal (WHO, 1967). These studies and the present data suggest an upper thermal limit of 40º C for A. lumbricoides. The lower thermal limit may be around 15º C because studies in South Africa have shown that the prevalence of both *A. lumbricoides* and *T. trichiura* are typically below 20% when the mean annual temperature is <15º C (Appleton & Gouws, 1996; Appleton et al., 1999).

N. americanus infection occurs practically wherever rural poverty and poor sanitation intersects with tropical climates, and in some parts of the subtropics (Bradley et al, 1993). It has been noted, however, that ancylostomiasis will occur in some areas where *N. americanus* L3 cannot survive during the winter months. This includes Anhui Province of China where temperatures will on occasion drop below freezing (Schad, 1990; Prociv and Luke, 1995; Yu, 1995; Wang et al, 1999). It has been postulated that the unique ability of *A. duodenale* L3 to undergo arrested development in the human host, may allow this species to survive during the cold winter months.

Season

In some endemic areas, soil-transmitted helminth infections exhibit marked seasonality. For hookworm, the phenomenom of arrested development explains why a pre-monsoon rise in fecal egg counts is sometimes observed in West Bengal and other areas (Schad et al, 1973). In some regions where marked rainy and dry seasons occur, hookworm transmission rates are higher during the former (Mark, 1975; Udonsi et al, 1980). In Saudi Arabia, a seasonal pneumonitis resulting from Ascaris migrations occurs annually from March to May (Gelphi and Mustafa, 1967). In Japan, seasonal fluctuations in Ascaris infection were attributed to annual application of nightsoil to crops (Crompton, 1989b)

Genetic Risk Factors

Overdispersion is a common feature of population distribution patterns for soil-transmitted helminth infections in humans (Williams-Blangero et al, 1997), leading some investigators to postulate that certain human populations may have increased genetic susceptibility. In West Bengal, epidemiologic studies have identified a population of individuals who are predisposed to acquiring heavy hookworm infections despite multiple exposures to the parasite and even anthelminthic chemotherapy (Schad and Anderson, 1985). A similar relationship was noted in Papua New Guinea (Quinnell et al, 1993; 2001). Predisposition has also been described for Trichuris infections (Bundy, 1986) and Ascaris infections (Thein Hlaing et al, 1987; Haswell-Elkins, 1987).

Predisposition to all three soil-transmitted helminthes may have either an immunologic, genetic or even a combined immunogenetic basis. For instance, some populations with low worm burdens in Papua New Guinea were noted to be relatively resistant to reinfection. Such individuals were noted to mount parasite-specific IgE and eosinophilic responses (Quinnell et al, 1995; Pritchard et al, 1995; Faulkner et al, 2002). In one case, an association was noted between hookworm-specific IgM responses and diminished prevalence and intensity (Xue et al, 2000). However, neither association could be identified for Ascaris infections in Bangladesh (Palmer et al, 1995). In some cases immunoglobulin levels appear to closely parallel worm burdens (Haswell-Elkins et al, 1989). This is particularly true of IgG4 host antibody responses (Palmer et al, 1996; Xue et al, 2000)

Using a variance decomposition approach it was estimated that the heritability of hookworm load in Zimbabwe was 37, indicating that 37% of the variation in quantitative hookworm egg counts is attributable to genetic factors (Williams-Blangero et al, 1997). Similarly, a variance component analysis implicated a genetic componen that accounted for between 30-50% of the Ascaris worm burden in eastern Nepal (Williams-Blangero et al, 1999), and 28% of the Trichuris worm burden both in Nepal and in Jiangxi Province, China (Williams-Blangero et al, 2002). Initial results of a genome scan of a genetically isolated Nepalese populations localized susceptibility to Ascaris infection to two genes, one on chromosome 1 and another on chromosome 13 (Williams-Blangero et al, 2002), providing the first evidence that individual quantitative trait loci may influence variation in a soil-transmitted helminth burden.

Behavior, Occupation And Socioeconomics

Specific occupations and behaviors influence the prevalence and intensity of soil-transmitted helminth infections. Because of the high rates of hookworm infection among adults, occupation probably has a greater influence on hookworm epidemiology. Engagement in agricultural pursuits remains a common denominator for human hookworm infection. Heavy infections in Sichuan Province, China and in Vietnam, for instance, are attributed to widespread use of feces as nightsoil fertilizer (Humphries et al, 1997; Hotez, 2002), whereas in other parts of Asia (e.g., Hainan) and other parts of the world, high rates of hookworm occur despite the absence of nightsoil use. Hookworm has been noted to target families who are involved with agricultural pursuits. The Chinese nationwide survey of 1988-1992, for instance, found the highest prevalence among vegetable growers and farmers (Hotez et al, 1997). In China, hookworm rates are the highest families that harvest sweet potato and corn (Sichuan Province), but also tobacco, cotton, soybeans, and rapeseed. In India, Bangladesh, and Sri Lanka high rates of infection are observed among workers and their families in the tea gardens, while high rates in Latin America occur among banana growers and on the coffee fincas. Plantation-style agriculture is a particular set-up for endemic hookworm infection (Sorensen et al, 1994). Along with malaria, and its associated genetic polymorphisms, hookworm is considered one of the major so-called "agriculture-related anaemias" (Fleming, 1994; Stoltzfus et al, 1997). Hookworm is generally not considered a water-borne infection. However in at least one instance in the Niger Delta of Nigeria, this mode of transmission was linked to high rates of infection among fishermen (Udonsi, 1988; Udonsi and Amabibi, 1992).

Several studies have investigated the effect of socioeconomic status in both rural areas and urban areas, and a recurrent finding of studies is that there is no consistent association. For example, work in Madagascar show that ascaris worm burden is more influenced by ethnicity and sex than socio-economic factors (Kightlinger et al 1998. This is in contrast to studies in Panama, which show significant associations (Holland et al 1988). In the urban setting of Lubumbashi, Zaire, factors related to poor sanitation were important in areas of low socio-economic status, but not high socioeconomic status (Tshikuka et al. 1995). The role of sanitation has traditionally been noted to have a major influence on the prevalence and intensity of soil-transmitted helminthes and will be discussed under control. Also important is the density of people in the house (Haswell-Elkins et al., 1989) and household clustering (Forrester et al 1988).

The impact of shoes and other footware on interrupting hookworm transmission has probably been overestimated, given that *N. americanus* infective larvae penetrate all aspects of the skin and *A. duodenale* larvae are orally infective. In Hainan, shoes were observed to have no impact on preventing transmission and may have even been a risk factor (Bethony et al, 2002).

Ethnicity and Culture

In a few well-documented instances, an apparent relationship between prevalence, worm burden and ethnicity have been described. This includes higher rates of Ascaris infection among more sedentary Bantus compared with Pygmies in the Central African Republic, as well as higher rates of infection in Malay or Indian people in Malaysia compared with the Chinese (Crompton, 1989b). In India, Nawalinski et al (1978) found a greater prevalence of hookworm among Muslims compared to Hindus despite their observation that both groups live in proximity to each other and that their behavior with respect to risk factors ordinarily attributed to soil-transmitted helminth infections did not appreciably differ.

Family and Housing

Ascaris prevalence and worm burdens have been noted to be higher among children from large families (Prakash et al, 1980). The order in which a child is born into a large family may also affect his likelihood of becoming infected (Adekunle et al, 1986). In Panama, houses made from wood and bamboo associate with significantly higher rates of soil-transmitted helminth infectins than concrete houses (Holland et al, 1988).

Food

Although not classically considered food-borne illnesses, Ascaris eggs and hook-worm larvae will adhere to vegetables and, if they have not been adequately composed for subjected sewage treatment, are then readily distributed in food markets. A survey from Japan found that at one time Ascaris eggs were present on 1178 of 2750 items of vegetables sold in 40 Tokyo shops (Kobayashi, 1980). Children living in an area of Marrakesh, Morocco where raw sewage Is used for agricultural irrigation were shown to have significantly higher prevalence of Ascaris and Trichuris infections when compared to a group of children where this was not a common practice (Bouhoulm and Schwartzbrod, 1997).

3. **Age, Gender and Geographical Burden: Mortality & DALYs**

Age

Emerging evidence suggests that human hookworm infections exhibit distinct age-dependent epidemiological patterns compared to Ascaris and Trichuris infections (Bundy, 1990; Chan et al, 1997; Pritchard et al, 1990; Quinnell et al, 1993; Needham et al, 1998; Bradley et al, 1992).

Ascaris and trichuris

When cross sectional surveys are carried out in areas where ascariasis and trichuriasis is endemic and sample sizes are adequate, three patterns become evident. First, prevalence rises rapidly once infancy has passed and tends to remain high. Second, intensity rises rapidly and peaks during childhood (among 5 – 15 year-olds) before declining steadily (Figure 1). Third, the frequency distribution of numbers of worms per host is overdispersed (Crompton, 2001).

Numerous examples of thse patterns have been collated and examined by Anderson and May (1991) who have developed a mathematical framework for explanation of the population biology of *A. lumbricoides* and other soil-transmitted nematodes. As a result of this framework there is universal recognition that the intensity of infection is the key variable to be studied if transmission, parasite population regulation, and morbidity are to be explained and manipulated for the benefit of individuals and communities (Crompton, 2001).

Prevalence data indicate the proportion of individuals infected but do not provide a simple indication of the numbers of worms harboured. The most important difference between the prevalence and age intensity profiles in ascariasis becomes apparent after peak intensity has been reached at about 5 – 10 years of age. Intensity then declines markedly and remains at low levels throughout adulthood, whereas prevalence rates remain high. This is in contrast to hookworm infections where more adults are typically infected, and have larger worm burdens. In a few regions, such as Burma and Iran, high Ascaris worm burdens have been described in adults (Crompton, 1989b)

Analysis of age-stratified data from 39 publications on the prevalence of intestinal nematode and schistosome infections in Africa has demonstrated that there is a remarkably consistent relationship between community prevalence and school-age prevalence for any given parasite species (Guyatt et al, 1999). For *A. lumbricoides* it would appear that prevalence data based on surveys of school-aged children overestimate the community prevalence of infection by 8 – 10%.

Hookworm

While heavy hookworm burdens still occur among children in some tropical areas (Stephenson et al, 1989; Labiano-Abello et al, 1999), in most of the world studied to date the peak prevalence and infection intensities for hookworm occurs in individuals in middle age, or even over the age of 50 (Gandhi et al, 2001; Bethony et al, 2002).

Shown in Figure 3 are the relationships between age and prevalence or age and intensity of two different helminth-endemic regions of China (Hainan Province) and Brazil (Minas Gerias State), respectively. These represent regions of high hookworm transmission and endemicity (Gandhi et al, 2001; Bethony et al, 2002), and show that the both prevalence and intensity increase as a function of age. Using a variance component model it was found that in Hainan Province, China, age accounted for 27% of the variation in quantitative egg counts and worm burden (Bethony et al, 2002). Figure 4 compares the age-related intensities of hookworm in both Hainan and Minas Gerias with other endemic helminth infections. In Hainan, Ascaris and Trichuris infections decrease after the age of 20, while in Minas Gerias the intensity of schistosomiasis diminishes after the age 10. This is in distinct contrast to hookworm epidemiologic patterns. Especially striking is the strong correlation ($r = 0.69$; $P < 0.001$) between age and eggs counts shown in Hainan as shown in Figure 3. In the Hainan study, a variance components analysis revealed that age and gender made the most important contributions to infection intensity (28-30%), with age alone responsible for 27% of this variation.   Similar patterns for infection have been observed in other *N. americanus* endemic areas in China (Liu et al, 1999; Zhan et al, 2000) and Southeast Asia (Humphries et al, 1997).

The mechanisms by which hookworms cause long-lasting chronic infections among the elderly are under active investigation. Of interest is a new finding that hookworm antigens may interfere with host lymphoproliferation and IL-4 levels among the elderly (J. Bethony and M.E. Bottazzi, unpublished observations) leading to the suggestion that this is an active process as a result of hookworm secreted antigens.

The association between increasing age and increasing prevalence and hookworm burden reveals an important public health problem for developing countries, as the elderly are seldom mentioned as a group either at high-risk for infection or the consequent morbidity associated with high worm burdens. The influence of aging on the prevalence and intensity of Necator infection has important public health consequences. In some parts of the developing world, such as China, the elderly are one of the most rapidly expanding age groups (Hotez, 2002). The nutritional and “background” health status of the elderly in developing countries are often poor (Tucker et al, 2001), which makes them vulnerable to the morbidity associated with chronic and heavy hookworm infection. Furthermore, while developing countries are experiencing an unprecedented growth in the number of their elderly (Howson, 2000), they are still plagued with the diseases of the developing world (Holden, 1996; Lloyd-Sherlock, 2000). The observation of increased prevalence and intensity of Necator infection among the elderly of China and elsewhere points to the need for further study into the reasons for this emerging pattern of infection (Hotez, 2002).

Gender

It is commonly accepted that males are generally more susceptible to infectious disease than females (Goble & Konopka, 1973; Klein, 2000). The same is also true for parasite infections (Bundy, 1988; Zuk & McKean, 1996). In contrast, the overall prevalence of Ascaris infection has traditionally been considered higher among females compared with males, regardless of age (Crompton, 1989b). Crompton (1989b) points out that this phenomenon has been observed in widely diverse geographic regions of Africa, India, and Southeast Asia. The basis of this is unknown. Recent data and analysis (SEE BELOW) has questioned this dogma, however.

For hookworm, the role of gender is often more significant, but its impact varies depending on regions. Possibly this observation reflects the relatively high rates of hookworm among adults instead of children, and therefore, the importance of occupational exposure. For instance in Zimbabwe (Bradley et al, 1992), Zanzibar, Tanzania (Albonico et al, 1997) and Papua, New Guinea (Pritchard et al, 1990) males exhibit higher prevalence and worm burdens than females. In contrast, in South China (Gandhi et al, 2001; Bethony et al, 2002) and Vietnam (Needham et al, 1998) females exhibit higher hookworm burdens. In the case of Vietnam, elderly women were observed to be responsible for most of the nightsoil use and the higher intensity could be explained, in this instance on occupational exposure (Humphries et al, 1997). Gender-based differences in endemic regions may not always reflect occupational exposure, however. For example, in Hainan women exhibit a higher prevalence and intensity of hookworm compared to males despite the absence of nightsoil use (Gandhi et al, 2001; Bethony et al, 2002). Similarly Needham et al (1998) could not identify a behavioral risk factor in their Vietnamese study population.

Ancylostomiasis among women during pregnancy has important implications for possible lactogenic transmission to neonates; an estimated 44 million cases of hookworm occur during pregnancy worldwide (Bundy et al, 1995; Navitsky et al, 1998). Hookworm during pregnancy may be associated with a number of adverse fetal outcomes; it therefore represents a maternal child health issue. In China, hookworm is a major cause of disease burden in women of child-bearing age, where it exceeds Japanese encephalitis, malaria, and tetanus as significant causes of infectious diseases morbidity (Hotez et al, 2003). In some cases ancylostomiasis during pregnancy may be responsible for lactogenic transmission to neonates in China (Yu et al, 1995), in Nigeria (Nwosu, 1981) and possibly elsewhere (Prociv and Luke, 1995). In a single case report, *N. americanus* larvae were also observed in human milk (Setasuban et al, 1980), although it is generally believed that lactogenic transmission is more common during *A. duodenale* infection. In West Bengal, India, the appearance of gender-based differences in hookworm prevalence and intensity among children emphasizes the possible importance of sex as a risk factor for hookworm.

Meta-analysis techniques, commonly used in medical research, are having increasing application in the synthesis of parasitological data (Michael et al., 1994; Poulin, 1996; Sheridan et al., 2000). For example, Poulin (1996) employed a fixed effects meta-analysis to investigate whether there is a consistent host sex bias in infection with helminth infections among non-human hosts. This study indicated a tendency for infection prevalence to be higher in males in many types of host-parasite associations, particularly for nematode infections in birds and mammals. By contrast, intensity of infection showed no clear sex bias except for nematodes parasitizing mammals, differences in infection intensity being significantly male-biased. A possible explanation put forward by the author for the observed differences was the immunosuppression associated with male hormones.

Examining sex-differences in infection patterns among humans is complicated by sex-related differences in exposure. The relative contribution of exposure and resistance has been of interest to parasitologists for decades (Bundy, 1988; Bundy & Blumenthal, 1990). A literature search was made of studies included in the WHO atlas of human helminth infections (Brooker et al., 2000; 2003). This global resource contains over 5,000 independent cross-sectional surveys conducted since 1970, with a sample size greater than 30. To be included in the present analysis, prevalence and intensity values has to be based on the examination of at least 10 individuals of each sex, following criteria used by Poulin (1996). Data included in the present analysis were obtained from published studies from Africa and Asia (a complete list of sources is available on request) and yielded between 27-220 comparisons of prevalence, but fewer comparisons of intensity.

A potential bias in using published survey data is that small non-significant differences in infection between the sexes are unlikely to be reported. To overcome this potential bias we also examined raw data for 40,078 schoolchildren available from studies in Africa. These included data for 1,739 children from 25 schools in Kenya (Brooker et al., 2000); 16,383 children from 255 schools Cameroon (Ratard et al., 1990, 1991, 1992), 1,026 children from 20 schools in Chad (Beasley et al., 2002); 2,197 children from 30 schools in Ghana (Partnership for Child Development, 1998); and 8,293 children from 97 schools in Tanzania (Lwambo et al., 1999; Partnership for Child Development, 1998) and 10,419 children from 168 schools in Uganda (Kabatereine et al., 2001; unpublished).

Analysis follows that used by Poulin (1996) who employed a fixed effects meta-analysis (Hedges & Olkin, 1985). In brief, differences in prevalence were calculated using the following formula:

$$(p_f - p_m)(J)\text{, where}\quad J = 1 - \frac{3}{4(N_f + N_m - 2) - 1}$$

which is the difference between prevalence in females (Pf) and that in males (Pm) weighted by a correction for small sample sizes (J). Differences in intensities were computed as:

$$\frac{(I_f - I_m)J}{I_f}$$

which is the difference between the mean intensity in females (If) and that in males (Im) weighted by J (here denoting the number of infected individuals). Differences in intensity are expressed as a proportion of the intensity in females to standardize for the variability in the mean intensities recorded. If there is no sex bias in levels of infection, differences in prevalence and intensity are expected to be normally distributed around a mean of zero. Two-tailed t-test were used to compare values of the comparisons to the expected mean of zero. Frequency distributions of differences were compared with X^2 test.

In the analysis of published data prevalence of infection with hookworm (and schistosome infection) was significantly higher overall in males than females (Table 4), with more negative (male-biased) than positive (female-biased) differences in prevalence (Figure 5). By contrast, the prevalence of *A. lumbricoides* and *T. trichiura* showed no significant difference between males and females (Table 4), with remarkably little variation between the studies (Figure 5).

To remove the potential publication bias, analysis was also made on the raw data from studies in Africa. Only in Cameroon was there a significant difference between males and females for the prevalence of *A. lumbricoides* and *T. trichiura*, with prevalence highest in males (Table 5). Overall, there was no difference in the frequency distribution of positive and negative differences (Figure 5). Hookworm prevalence was significant higher among males than females in Cameroon, Ghana, Kenya, Tanzania (lake) and Uganda. *Schistosoma haematobium* was higher among males than females in Cameroon, Chad and Tanzania (lake), and *Schistosoma mansoni* was higher in males in Cameroon, Tanzania (lake) and Uganda (Table 5, Figure 5).

The meta-analysis supports a previous observation that males are at greater risk for hookworm infection (Bundy, 1988). However, notable exceptions to this finding were noted in South China (Gandhi et al, 2001; Bethony et al, 2002) and Southeast

Asia (Humphries et al, 1997). The observation that the prevalence of Ascaris infection is higher among females compared with males, regardless of age (Crompton, 1989), is not supported by the current meta-analysis.

Geographical Burden

Based on the relationship between prevalence and mean worm burden, a model was developed by Guyatt & Bundy (1991) that identified communities at risk from disease due to soil-transmitted helminth infections. The relationship is non-linear and determined by the frequency distribution of numbers of worms in the host population. For all human soil-transmitted helminths studied to date, which so far includes Ascaris, Trichuris, both hookworms, Enterobius, and Ternidens, worm burdens exhibit a highly overdispersed distribution so that most individuals harbor just a few worms in their intestines while a few hosts harbor disproportionately large worm burdens (Bundy, 1995). As a general rule, approximately 70% of the worm population is harbored by 15% of the host population. These heavily infected individuals are simultaneously are the major source of environmental contamination (Bundy, 1995). Heavily infected individuals are more at risk from morbidity and mortality and also act as significant contributors of potentially infective stages in the environment.

This work was expanded further by Chan et al (1994), who developed a model based on observed patterns of age-prevalence and geographical heterogeneity, and data on the observed prevalence of soil-transmitted nematode infections. This model was used to present an estimate of the numbers of infected individuals, along with estimates of numbers at risk of developmental consequences and more severe clinical consequences, for 6 of the 8 regions of the world defined by the World Bank for the Global Burden of Disease study. The model uses the negative binomial distribution to calculate the frequency distribution of worm burden between individuals. Morbidity estimates were made on the assumption that the risk of developmental consequences is higher in individuals with worm burdens about a certain age-dependent threshold and that more severe consequences are associated with larger worm burdens.

Ascaris and trichuris infections

A revised estimate of the probable number of Ascaris infections worldwide was made along with a better categorization of the morbidity due to ascariasis (de Silva et al 1997b). This disease classification is shown in Table 1. These estimates indicated that in 1990, about 1.3 billion individuals worldwide were likely to be infected with *A. lumbricoides*. About 59 million of these (including 51 million children below the aged of 15 years) were estimated to be as risk of faltering growth and or decreased physical fitness as a result of infection (see Table 1). About 1.5 million children were thought to probably never catch up the deficit in growth, even if treated. In addition to these chronic, insidious effects, about 11.5 million individuals (almost all of them children), were estimated to be at risk of more acute clinical illness. These figures also indicated annually at least 10,500 deaths are directly attributable to one of the serious complications of ascariasis; more than 90% of these deaths involve children.

This study also estimated that a little over half of all infected individuals are in China and the region then classified as “Other Asia and Islands” (see Table 2). About 60% of all individuals at risk of morbidity were also thought to live in the same regions. Prevalence in the Middle Eastern Cresent, India and SubSaharan Africa tended to be lower than in China and the rest of Asia. Thus the numbers at risk of morbidity in these regions are also low.

These estimates of numbers at risk of morbidity and death were subsequently translated into DALYs (Chan, 1997). The total DALYs lost due to ascariasis was estimated at 10.5 million for the year 1990.

New estimates that take into account population growth in endemic countries, as well as changes in prevalence that may have resulted from control activities implemented over the last decade, are now under preparation (de Silva & Brooker, unpublished). These indicate that the numbers of infected individuals and those at risk of morbidity have declined in Latin America and the Caribbean and in some countries of East Asia, due to declining prevalence rates. In the rest of the world, however, it appears that increasing population size combined with lack of widespread control measures have resulted in a sizeable increase in the number of infections, and in numbers at risk of morbidity and death.

Asia

- China

The national survey carried out in China in 1988 – 1992 found that almost half (47%) of China’s population was infected with ascariasis – an estimated 531 million individuals (Xu et al, 1995). The prevalence of trichuriasis was lower, with a national average of about 19%, and an estimated 212 million infections. Much higher prevalence rates were seen in the southeastern provinces that have a tropical / sub-tropical climate, compared with the northwestern provinces. Subsequent surveys carried out in Yunnan Province in the south, found that prevalence of ascariasis and trichuriasis remained high (Zhang et al, 2000). In Jiangsu Province, however, where rapid economic development has occurred, and a mass chemotherapy programme has been implemented, prevalence of ascariasis and trichuriasis was found to have declined dramatically (Sun et al 1998).

The national survey found that, as in other parts of the world, the highest prevalence rates occur among school aged children. The widespread use of human nightsoil as a major source of fertilizer in agricultural production is an important reason for the high prevalence rates seen in China. Thus students from primary and high schools had high prevalence rates, as did farmers and vegetable growers. The high prevalence among fishermen is attributed to the lack of sanitary facilities and unhygienic habits, since most of them lived along rivers or lakes, and were unable to settle down permanently (Xu et al 1995).

Low prevalence rates were found among herdsmen who live mostly in the low-endemic north-western provinces. Similarly, a survey carried out among 738 residents of rural areas near Ulaanbaatar, the capital of Mongolia, did not find any major soil-transmitted helminth infections (Lee et al, 1999).

- Southeast Asia

  A. lumbricoides and *T. trichiura* are present throughout Southeast Asia and exhibit distinct geographical patterns. The results of a national survey in Vietnam show that the prevalence of these species is highest in the Red River Delta Region of northern Vietnam and lowest southern districts (Anon., 1995; Brooker et al., 2003). High prevalences have also been described in the northern and southern regions of Myanmar (Thein-Hlaing, 1985), peninsular Thailand (Preuksaraj et al., 1983; Anantaphruti et al., 2000), central Lao PDR (Hohmann et al., 2001; Vannachone et al., 1998; Kobayashi et al., 1996), and Kratie and Stung Treng provinces in Cambodia (Urbani et al., 2001). Prevalence is lowest in the southern provinces of Vietnam and central provinces of Thailand (Anon., 1995; Brooker et al., 2003; Preuksaraj et al., 1983).

  All soil-transmitted helminths are widely distributed across Indonesia (Bakta et al., 1993; Bang et al., 1996; Higgins et al., 1984) and the Philippines. However, large scale control programmes have successfully reduced prevalence levels to less than 30% in some areas of Indonesia (Margono, 2001).

- South Asia

  The results of a survey conducted in 8 different ecologically homogenous zones in India have been published recently (Bora et al, 2001). The surveyed areas were in the plains (Bhiwani in Haryana State, Pune in Maharashtra and Chitradurga in Karnataka), on the western coast (Calicut and Allepey in Kerala), in the deserts of Rajasthan (Alwar and Jodhpur), and Gangtok in the hills of Sikkim. The sample population included schoolchildren in urban, rural and tribal areas. The highest prevalence of ascariasis was found in urban Chitradurga (39.7%), in rural Gangtok (30.8%) and in Calicut (25.7%). Prevalence of ascariasis was very low in Haryana and Rajasthan, which are both in the northeast of India. Trichuriasis was very low in most areas. The highest prevalence was seen in Calicut (25%) and Allepey (21.6%) in Kerala.

  Extremely high prevalence rates have been described among fishing communities in South India. Mani et al (1993) found that 91% of schoolchildren in a fishing community in Visakhapatnam had ascariasis and 71% had trichuriasis; similar prevalence rates were described by Elkins et al (1986) in a community in Vairavankuppam in Tamil Nadu. Latrine facilities in these communities are described as non-existent, and children were observed to defaecate and play in the school grounds.

  However, even within southern India, there appears to be a great deal of heterogeneity in transmission levels: a study carried out in 11 villages in Chingleput District found that only 2.1% of the residents had ascariasis, and 4.8% had trichuriasis, while 92% had hookworm (Srinivasan et al, 1987).

- *Bangladesh*: In contrast to India, much of Bangladesh seems to have a high prevalence of ascariasis and trichuriasis. A study of 1765 residents of a suburb of Dhaka, the capital of Bangladesh found that 89% had ascariasis, with a mean worm burden of 18.5 (Hall et al, 1992). Follow-up surveys found rapid re-infection after treatment with pyrantel pamoate, although prevalence rates and worm burdens declined slowly. The prevalence of trichuriasis among 5 – 10 year olds in this community was 92.6% (Hall & Nahar, 1994).

  In the rural Jamalpur District of northern Bangladesh, which is subject to annual flooding, 71% of 2 – 6 year old children were found to have ascariasis; 44% had trichuriasis, while only 10% had hookworm (Rousham & Mascie-Taylor, 1994). Similarly high prevalence rates were found in a study that covered 4 discrete geographic areas, all located within a radius of 80 km from Dhaka (Mascie-Taylor et al 1999).

- *Nepal:* The transmission of all three major soil-transmitted helminths is common in the southern rural plains of Nepal that border India (the terai). Prevalence rates of 47-51% ascariasis have been reported among children aged 1 – 10 years living in this area (Curtale et al, 1993, Curtale 1995). In Sarlahi District, also in the terai region, 56 – 60% of pregnant women were found to be infected with *A. lumbricoides* (Navitsky et al, 1998, Dreyfuss et al, 2000). The prevalence of trichuriasis was less than 10% in this population.

- *Sri Lanka:* Wide-spread public awareness of intestinal nematode infections, and anthelmintics have contributed to declining rates of all three soil-transmitted helminth infections in much of the country. Transmission remains a problem, however, in the tea and rubber estates, where housing and sanitary facilities are usually highly inadequate (Sorensen et al, 1996). A biannual mass chemotherapy programme that targets school aged children has been in effect in this sector since 1994 and prevalence rates have declined steadily (Ismail et al, 2001). The other high-risk population consists of urban slum dwellers, but even among these, declining prevalence rates have been noted (de Silva et al, 1996, de Silva et al, 1997, Udayani et al, 1999).

- Subsaharan Africa

Poverty and poor sanitation mean that Ascaris and Trichuris are common throughout much of sub-Saharan Africa, with climatic factors influencing the broad-scale distribution of these parasites.

In West Africa for example, there appears to be a geographical trend with prevalence greatest in the tropical areas of southern Cameroon (Ratard et al., 1991) and southwestern Nigeria (Holland & Asaolu, 1990). These areas, where prevalence rates exceed 70%, are characterised by annual rainfall exceeding 1400mm (Prost, 1987) and an absence of extreme temperatures (Brooker & Michael, 2000). Elsewhere in West Africa, similar gradients in distribution are also found. In Guinea, prevalence is highest in the Guinean forest areas, where prevalence reaches 30%, compared to elsewhere in the country where prevalence is <5% (Gyorkos et al., 1996; Montresor et al., 1997). High prevalences also characterise the equatorial areas of Cote d'Ivoire (Haller, 1980; Nozais et al., 1979) Gambia (Palmer & Bundy, 1995), Ghana (Partnership for Child Development, 1998), Liberia (Sturchler et al., 1980), Sierra Leone (Boyah et al., 1993; Gbakima et al., 1994), and Senegal (Salem et al., 1994). Within these regions however, there exists marked variation in infection patterns, which is suggested to reflect small-scale differences in personal hygiene and behaviour, as well as microhabitats (Crompton, 1987).

In areas where rainfall falls below 1400mm and temperatures exceed 37-40 °C, there is usually an absence of transmission as demonstrated by studies in Chad (Brooker et al., 2002), Mali (De Clerq et al., 1995), Mauritania (Urbani et al., 1997) Niger (Develoux et al., 1986), and Sudan (Magambo et al., 1998).

Ascaris and trichuris are widespread in Ethiopia but with prevalence rates varying considerably: rates are lowest in the low and dry areas of the country than in the more more humid highlands (Tedla & Ayele, 1986 ; Jemaneh, 1998). In East Africa, prevalence rates tend to be lower in the relatively drier and less humid coastal areas than elsewhere. In the hot dry areas of Somalia for instance, prevalence is <5% (Peltola et al., 1988), whereas in the more humid southern areas the prevalence of ascaris is 14-33% and the prevalence of trichuris is 59-79% (Peltola et al., 1988; Ilardi et al., 1987). In coastal areas of Kenya prevalence is typically 20-30% (Ashford et al., 1992 ; Magnussen et al., 1998), and similar prevalences are also found in coastal Tanzania (Partnership for Child Development, 1998). In contrast, prevalence exceeding 50% is common in the heavily populated areas east of Lake Victoria in Kenya (Olsen, 1998; Brooker et al., 2000) and southern areas of Uganda (Kabatereine et al., 2001). Prevalence of <5% are typically found in the less populated and drier areas south of the Lake Victoria (Lwambo et al., 1999).

In Southern Africa where annual rainfall typically falls below 1000 mm, negligible prevalence are found. For example, prevalence rates of <5% are found in northern Malawi (Randall et al, 2002) and Zimbabwe (Chandiwana et al, 1989).

Ascaris and trichuris are also common on Madagascar, but prevalence vary throughout the island with prevalence highest in the rainforest areas (Kightlinger et al., 1995 ; Hanitrasoamampionona et al., 1998).

- Middle East and North Africa

The prevalence of soil-transmitted helminth infections tends to be low in much of the Middle East and North Africa, probably because the hot, dry climatic conditions that prevail in much of the region are unsuitable for survival of eggs and larvae.

In Algeria, on 1.5% of 11,601 individuals living in and around Algeria were found to have ascariasis, while only 2.8% had trichuriasis, and none had hookworm (Bachta et al, 1990). In Morocco, a survey that examined 1682 individuals from 3 provinces found that less than 5% had ascariasis; trichuriasis was of even lower prevalence and hookworm was not seen at all (El Idrissi et al, 1999). In another, earlier study carried out in 3 other provinces of Morocco, slightly higher prevalence rates were found: 2.8 – 11.5% for ascariasis and 7.0 – 24.9% for trichuriasis (Jimenez-Albarran & Odda 1994). Similar rates are described from Egypt (Curtale et al, 1998, Hassan, 1994), Iraq (Mahdi et al, 1993) and Saudi Arabia (Al-Shammari et al, 2001, Omar et al, 1991).

Even within the Middle East however, high prevalence rates have been reported from some countries. For example, in Hamadan Province, Iran, the prevalence of ascariasis was found to vary between 41 – 76% before the initiation of a mass chemotherapy programme (Fallah et al, 2002). The prevalence of trichuriasis was much lower (0 – 19.6%). A high prevalence of ascariasis (61%) and trichuriasis (21%) has also been reported from Yemen (Raja'a et al, 2001).

- The Americas

The prevalence of soil-transmitted helminth infections in Brazil and Mexico, the two countries with the largest populations in this region, have declined over the last few decades. A study that compared prevalence rates in two household surveys (the first undertaken in the mid-1980's and the second in the mid-'90s) in Sao Paulo City, Brazil, found a significant decline in the prevalence of both ascariasis and trichuriasis (Ferreira et al, 2000). Both infections were found in less than 5% of the study population in the second survey. The decline in prevalence was attributed to improved family income, maternal schooling, housing, sanitation and access to health care. Relatively low prevalences have also been described in the 1990's from the cities of Caparaó and Alto Caparaó (Carneiro et al, 2002) and Ortigueira (Scolari et al 2000). Higher rates of 25 –30% have been reported from the cities of Rio de Janeiro (Campos et al, 2002) and Salvador (Prado et al, 2001), but these rates are still much lower than those described in the 1960's (Vinha 1971). A very high prevalence of ascariasis (88%) was found recently among residents of an indigenous reserve, but the prevalence of trichuriasis in this community was only 2% (Scolari et al, 2000).

With regard to Mexico, a recent review of studies carried out between 1981 and 1992 concluded that the prevalence of ascariasis is about 11% and trichuriasis about 2% (Tay et al, 1995). This contrasts greatly with prevalence rates of over 60% in the 1960's (Stoopen, 1964). Argentina and Chile also have relatively low prevalence rates, except in areas with extremely poor sanitation, probably due to their climatic conditions (Gamboa et al, 1996, Lura et al, 2002, Mercado et al, 1997, Oberg et al, 1993, Torres et al, 1997, Navarrete & Torres 1994, Mejias, 1993).

High prevalence rates are still seen, however, in Bolivia and Ecuador. In the Amazonian lowlands of southeastern Bolivia, prevalence rates of 60 – 80% have been found to ascariasis, and rates of up to 76% for trichuriasis (Lagrava, 1986). In the highlands, where the altitude exceeds 3000m, prevalence rates are much lower: 1 – 15% for both ascariasis and trichuriasis (Lagrava, 1986, Flores et al, 2001). Studies have been carried out in a variety of ecological zones in Ecuador as well. These include the Esmeraldas Province on the Pacific coast (Cooper et al, 1993), the city of Portoviejo (Andrade et al, 2001), mountainous villages (Levav et al, 1995), and indigenous populations in the Amazon basin in the northeast (Sebastian & Santi 2000). Prevalence rates for ascariasis range from 50 – 65% and from 6 - 50% for trichuriasis in these studies.

Among the tropical countries of Central America, high prevalence rates have been reported for ascariasis and trichuriasis in Guatemala (Anderson et al, 1993, Watkins et al, 1996) and in neighbouring Honduras (Smith et al, 2001), but lower rates of both infections (10 – 15%) have been reported from the city of Leon in Nicaragua (Tellez et al, 1997). Many of the Caribbean islands also have high prevalences of ascariasis and trichuriasis; often much more trichuriasis than ascariasis (Bundy 1986, Beach et al, 1999, Wong et al, 1994).

Hookworm

Necator americanus is the predominant hookworm worldwide in the tropics and subtropics, except in some defined locations where *A. duodenale* is focally endemic. The major *N. americanus* endemic regions include South and Southwest China, South India, Southeast Asia, Subsaharan Africa, and Central and South America. The *A. duodenale* predominant regions include more northerly latitudes of South and West China (e.g., Anhui, Sichuan Provinces) and India (e.g., Kanpur) where *N. americanus* cannot survive the relatively harsh conditions, Egypt, Northern Australia and in a few localities in Latin America including Northern Argentina, Paraguay, Peru, and in a region border El Salvador and Honduras (Hotez and Pritchard, 1995). Throughout the world, mixed infections with both major hookworm species are common.

Asia

- China. In the 1940s, a Rockefeller Foundation-sponsored studied hookworm infection in rural Sichuan (southwestern China), where they observed hookworm infection in almost 100 percent of the population. The commission noted that both major species of hookworm were present and were a particular public health problem among families connected to the farming and cultivation of certain crops such as corn and sweet potato (Chang et al, 1949). This is in contrast to the findings of an earlier China Hookworm Commission sent to Jiangsu and Guangdong in eastern and southeastern China respectively, which attributed hookworm to the cultivation of mulberry trees used in sericulture for the silkworm industry (Cort et al, 1926). For centuries, hookworm plagued the poor rural areas of southern and southwestern China either because of the practice of indiscriminate defecation or, more commonly, because Chinese farmers relied on human waste (nightsoil) for fertilizer. It was known as huang zhong bing (the “yellow puffy disease”). Absence of progress in solving modern China’s hookworm problem became starkly evident following a nationwide survey of human intestinal parasites. From 1988 to 1992 the Chinese Ministry of Health in association with provincial and national institutes of parasitic diseases, as well as local anti-epidemic field stations conducted fecal examinations on 1,477,742 individuals living in 2,848 study sites in 726 counties (Yu et al, 1994; Xu et al, 1995; Hotez et al, 1997). The nationwide survey found that an impressive percentage of China's population is infected with helminthes. Approximately 17 percent were shown to harbor hookworms, indicating that by 1992 there were an estimated 194 million cases of hookworm in China. Based on measured determinations of daily blood loss caused individual hookworms, the overall yearly blood loss resulting from China's hookworm burden was equivalent to the amount of blood donated by more than 80 million individuals, or more than one million blood donors every week! The survey identified hookworm as a public health threat in the same agriculturally rich provinces along the Yangtze that were identified prior to the Liberation as hookworm problem sites in South and Southwest China. The nationwide survey found that 40 percent of Sichuan and 20 percent of Jiangsu were infected with hookworm. Approximately one-quarter of the hookworm infections were moderate or heavy enough to result in clinically significant effects. The tropical South China Sea island province of Hainan exhibited the greatest hookworm prevalence, with approximately 60 percent rates of infection.

As shown in Table 3, the rates of hookworm in the highly endemic regions have changed little since the survey was completed in 1992, when they were reinvestigated in 1997-98 (Hotez, 2002). Hainan, Sichuan, Yunnan, and Anhui remain highly endemic for hookworm. Hainan alone loses an estimated 1 million liters of blood annually from hookworm infections. It was observed that the middle-aged and elderly populations over the age of 50 constituted the most infected population extended to every village examined in Anhui, Hainan, Jiangsu, Sichuan and Yunnan (Table 3). In the regions investigated between 1997 and 1998, Hainan and Yunnan exhibited an overwhelming predominance of *N. americanus* infection (Gandhi et al, 2001; Bethony et al, 2002; Zhan et al, 2000), while *A. duodenale* was the predominant hookworm in Anhui (Wang et al, 1999). Generally speaking, *N. americanus* is the predominant hookworm south of the Yangtze River, while *A. duodenale* predominates in a belt just north of the Yangtze. Hence, northern Jiangsu is predominantly infected with *A. duodenale*, but *N. americanus* increases further south (Sun et al, 1998). Mixed infections occur in Sichuan Province (Liu et al, 1999).

The observation that hookworm is predominantly a disease among China's middle-aged and elderly has important implications for the nation's rapidly changing demographics. China, like much of the developing world, is anticipated to experience rapid expansion of its geriatric population. China's population is aging rapidly. For example, it took over a century for France's elderly population to double from seven to 14 percent of its population, whereas China is expected to double the equivalent population within 25 years (Peterson, 2001). By the year 2020 it is estimated that 11 percent of China's population will be over the age of sixty-five (Peterson, 2001). The rapid increase in the number of elderly in the hookworm-endemic regions of Anhui, Hainan, Sichuan, Yunnan, and elsewhere in South China may create a new populations susceptible to hookworm. Over the next decade hookworms could flourish in the intestines of this new graying Chinese population.

- Southeast Asia. Hookworm occurs throughout the region in no clear pattern (Anon., 1995; Brooker et al., 2003; Preuksaraj et al., 1983). Moderate prevalences (20-49.9%) are found in central Thailand and some areas of Vietnam (Needham et al, 1998); other provinces in Vietnam and southern Thailand as well as parts of Cambodia (Urbani et al., 2001) have high prevalence.

  Nearly 100% of adults are infected with *N. americanus* on Karkar Island, Papua New Guinea (Pritchard et al, 1990; Pritchard, 1995). The intensity of infection is related to host age, and the development of anaemia is believed to occur here than at lower levels than previously reported elsewhere. In Karkar a negative correlation has been noted between host IgE and eosinophilia with the weight and fecundity of *N. americanus* (Quinnell et al, 1995; Pritchard et al, 1995), suggesting that the immune response does have some effect on *N. americanus* infection. Because of the similarity between pre-treatment and post-treatment hookworm rates (Quinnell et al, 1993; Pritchard, 1996; Quinnell et al, 2001), it is believed that host predisposition to hookworm infection occurs here.

- South Asia. A recent survey in India reported very low rates of hookworm infection in all eight ecological zones surveyed (Bora et al, 2001). The highest prevalence was 6.6% in the urban areas of Alwar, in the desert state of Rajasthan, followed by 3.9% in Allepy on the southeastern coast. However, much higher prevalence rates have been reported in other studies of individual communities, particularly those carried out in the state of Tamil Nadu in the south. A survey of 1348 individuals living in 11 villages of the Chingleput District in Tamil Nadu found 92% to be infected with hookworm (Srinivasan et al, 1987). Although most (96%) had light infections with egg counts of less than 2000 epg, 80% of adult males, 87% of adult females and 90% of children were anaemic, and there was a significant association between egg counts and haemoglobin levels. This study did not find a difference in the intensity of infection between those engaged in agriculture and those who were not, but those who lived in temporary housing with mud floors had higher egg counts than those in semi-permanent or permanent housing.

  Two separate studies carried out in fishing villages in Tamil Nadu have also reported relatively high prevalence rates (40 – 15%) for hookworm (Mani et al, 1993, Haswell-Elkins et al, 1988). The study carried out in Jalaripet found that infected schoolchildren expelled both *N. americanus* and *A. duodenale*, but the former was about 5 times more common (Mani et al, 1993). A survey of tribal schoolchildren in Madhya Pradesh found that the prevalence rates among the three tribes surveyed ranged from 6.5% to 26.8% (Chakma et al, 2000); no species identification was carried out in this survey.

  In Nepal, hookworm infections have been found to contribute significantly to anaemia among children and women living in the southern plains that border India (Curtale et al, 1993, Dreyfuss et al, 2000). However, in this terai region, only one species of hookworm (*A. duodenale*), has been described to date (Navistky et al, 1998). This is consistent with other studies that have shown ancylostomiasis to be the species usually found in the more northern regions of the tropics.

- Subsaharan Africa

Mixed infections of hookworm are common throughout Subsaharan Africa. Unlike, Ascaris and Trichuris, hookworms have a wider distribution occurring throughout sub-Saharan Africa. However, available epidemiological studies suggest that hookworm prevalence varies across the continent in no clear pattern. This is demonstrated by national surveys for Cameroon (Ratard et al., 1992), Uganda (Kabatereine et al., 2001) and Zambia (Wenlock, 1979). Estimates of prevalence vary considerably, and range from 10-100%.

Where hookworm is limited is in the Sahelian regions of Chad (Brooker et al., 2002), Mali (De Clerq et al., 1995), Mauritania (Urbani et al., 1997) and Niger (Develoux et al., 1986), and the dry and less humid areas of East Africa (Hall et al., 1982). Within these areas however, the parasites can occur more locally; in Mali for example prevalence reaches 86% in Sikasso Region (Behnke et al., 2000).

In Ethiopia, the overall rate of hookworm is estimated to be 22%, with prevalence decreasing with increasing altitude (Tedla & Jemaneh, 1985; Jemaneh, 1998), with hookworm virtually non-existent in areas above 1000m elevation. A similar altitude gradient is evident in South Africa (Appleton & Gouws, 1996).

Two of the best-studied regions with respect to the modern investigative epidemiology of hookworm over the last decade have taken place in Pemba Island, United Republic of Tanzania and in Zimbabwe.

  - Tanzania. Pemba Island is the smaller of the two islands of Zanzibar, United Republic of Tanzania. It is densely populated with a humid tropical climate. The island is under intense investigation by the Communicable Disease Division of the WHO, where there is a high prevalence of all three soil-transmitted helminthes, schistosomiasis (S. haematobium) and holoendemic malaria (Albonico et al, 1997; 1998; Booth et al, 1998; Stoltzfus et al, 2001). The prevalence of hookworm Pemba reaches 94% among some populations. Mixed infections occur on Pemba with 65% infected with N. americanus exclusively, 2% with A. duodenale exclusively and 27% with mixed infections (Albonico et al, 1998). On the mainland, hookworm is prevalent through the country (Lwambo et al., 1992), including coastal regions (Partnership for Child Development, 1998), lake regions (Lwambo et al., 1999) and central regions (Booth et al., 1998).

    Hookworm infections, as well as schistosome-associated hematouria are more prevalent in boys, and more prevalent in rural parts of the island (Albonico et al, 1997). Studies in Pemba confirm that infection with A. duodenale in children and heavy transmission of A. duodenale is associated with a greater burden of iron-deficiency anemia than infection with N. americanus (Albonico et al, 1998). Iron supplementation linked to hookworm anemia was noted to improve motor development in some children with heavy infections (Stoltzfus et al, 2001).

- Zimbabwe. In two regions of Zimbabwe studied in the early 1990s, the Burma Valley and the Kariba eastern basin, N. americanus was the exclusive hookworm recovered, although a related nematode Ternidens deminutus is also present (Bradley, 1990; Bradley et al, 1992; Bradley et al, 1993). The prevalence and intensity of hookworm in Zimbabwe rapidly approaches 50-60% by 5 years of age and then increases at a diminished rate, so that 70-80% of the population over the age of 45 is infected. The steady rise in prevalence and intensity with age, contrasts with the convex patterns observed for Ascaris and Trichuris. By administering an anthelminthic drug and recovering the adult hookworms it was determined that the burdens range from 0 to 70 worms per individual, with a classic overdispersion pattern (10% of the hosts harboring 90% of the parasite population), and a negative binomial distribution. Mixed infections are common throughout Subsaharan Africa. Two of the best-studied regions with respect to the modern investigative epidemiology of hookworm over the last decade have taken place in Pemba Island, United Republic of Tanzania and in Zimbabwe.

- The Americas

In some regions of the Americas, the epidemiologic patterns of hookworm differ from those seen in Asia and Africa, with some villages reporting high rates of infection among children and adolescents.

- Central America. Hookworm is a major infection in Central America, particularly in impoverished rural areas. During the 1970s Max Bloch and his colleagues identified hookworm in 40% of the residents of El Salvador and estimated that 75,600 patients suffer from clinical hookworm disease and anemia (Bloch and Rivera, 1977). Similar rates of infection were at one time endemic to Costa Rica, Honduras, and presumably elsewhere (Hunter et al, 1968; Hoekenga, 1950). Although *N. americanus* is the predominant hookworm in Central America, a pocket of ancylostomiasis is believed to be present in El Salvador (Bloch and Rivera, 1977), as well as in Choluteca on the Honduran-El Salvador border (Girard de Kaminsky, personal communication). The distribution of hookworm infection was recently investigated in two endemic regions of Honduras (Bottazzi et al, 2002 unpublished). Atlantida on the northern Atlantic Coast is populated by both Latino and African-American (Garifuno) populations. The overall prevalence in two different municipalities (Tela and Progresso) is 45%, with higher prevalence among males (50%) than females (42%). Among the former, the prevalence of hookworm increased with age up until approximately the age of 30 and subsequently reached a plateau, whereas among females the prevalence remained constant across age strata. In one of the municipalities (Tela), it was found that the majority of cases occurred in children and adolescents, much like Ascaris and Trichuris infections. In Choluteca, the prevalence of hookworm was low (less than 8%), with no obvious age or sex distribution.

- Paraguay and Brazil. Hookworm was first identified as an important pathogen in Paraguay in the 1920s when Fred Soper detected an overall prevalence of 98% (Soper, 1927). Of interest, was the finding that *A. duodenale* was the predominant species among isolated indigenous groups west of the Paraguay River, whereas *N. americanus* predominated in the east. Soper speculated that A. duodenale was the indigenous species, but was gradually displaced by *N. americanus* when it was introduced by Brazilian troops during the War of the Triple Alliance (1865-70). Hookworm continues to be present in areas of Brazil. For instance a study in Minas Gerias found hookworm prevalence to be 57% (Webster et al, 1997), *N. americanus* predominating. However, *A. duodenale* is also endemic in Brazil. In a cross-sectional study in Itagua, Paraguay in which 192 people were tested for the presence, intensity and species of hookworm, 59% were found to be infected (Labiano-Abello et al, 1999). However, unlike patterns seen in Asia, the highest prevalence occurred among young adults (20-29 years), while intensity hookworm infections were clustered between the ages of 5 and 14 years. No differences were seen between genders. Both *N. americanus* and *A. duodenale* were identified, although the former species predominated.

4 Impact on the Poor

Asaris and Trichuris

Ascariasis and trichuriasis, along with the hookworms, are essentially diseases of poverty, since safe disposal of human faeces necessarily interrupts transmission. Throughout the tropics, wherever climatic conditions permit the development and embryonation of eggs in the soil, the relationship between poverty and soil-transmitted helminth infection has been noted. However, individual factors that influence transmission in a given community are often highly local in nature. For example, a study carried out in West Java, Indonesia found prevalence and intensity of ascariasis and trichuriasis to be closely related to socioeconomic conditions (Pegelow et al, 1997). Children who had a latrine at home, lived in homes with an electricity supply and a cement floor, who took their baths at home, defecated at home, and always wore slippers had low prevalence rates, whereas those who washed themselves at a well or spring, and defecated in a hole around their houses had high prevalence rates. In Malaysia, a study that investigated the prevalence of Ascaris and Trichuris infections among pre-schoolchildren in various socio-economic sectors found infection to be more common in the disadvantaged: those living in urban slums, rural fishing and farming communities, and rubber and oil-palm estates (Kan et al, 1993). A study that examined children from 5 different communities in Madras, India, found that prevalence rates and intensities were much higher in the fishing villages where children did not use latrines, walked barefoot, and drank unprotected well water, when compared with children from an elite community that had homes with flush toilets and pipe-borne water supplies (Elkins, 1984). In Sri Lanka, the highest prevalence rates are now seen among those living in the tea and rubber estates, which continue to have highly inadequate sanitation and hygiene (Sorensen et al, 1996). Income and literacy levels in these communities are among the lowest in the country. Two studies carried out in poor urban communities in Sri Lanka have both shown significant correlation between socioeconomic factors and the prevalence of ascariasis and trichuriasis (de Silva et al, 1996 and Ismail et al 1988).

Similar findings have been reported from the Americas. As study of ascariasis and trichuriasis in relation to socioeconomic variables in 4 rural communities in the Honduras found that prevalence of both infections related, among other factors, to the lack of a latrine and defecation in a site other than a latrine (Smith et al, 2001). In a study carried out in two adjacent, but socio-economically distinct, urban communities in Costa Rica, prevalence of STH infection was found to be significantly higher in the squatter settlement than in the other community, which had access to modern sewage facilities (Kosoff et al, 1989). Attempts have even been made to develop environmental health indicators for use as a basis for preventive measures against ascariasis in Brazil (Carneiro et al, 2002). The results of this study showed the protective effects of the availability of water for washing in particular, and better hygiene, sanitation and socio-economic status in general. The interactive effect of crowding was found to be five times larger in households without water in the washbasin than in those having water.

Hookworm (Adapted From Hotez, 2002)

Hookworm is also intimately linked to poverty and economic underdevelopment. Probably more than any other single factor, including sanitation, administering anti-parasitic drugs, wearing barrier protection, and health education, economic development has done the most to control or eradicate hookworm among the industrialized nations (Hotez, 2002). While it is widely assumed that Rockefeller Foundation-sponsored interventions were responsible for eradicating hookworm, malaria and yellow fever from the southern United States during the early 20th century, almost certainly it was the overall economic development of the new South that finally chased away the hookworms and the disease-carrying mosquitoes. Similar economic reforms that transformed South Korea during the 1960s and 1970s, helped to eradicate the soil-transmitted helminthiases from this region (Hotez, 2002).

Because the decade of the 1990s has been one of the most productive periods in China's modern economic history, it was of interest to determine how China's transition to a modern economy affected prevalence rates of endemic hookworm (Hotez, 2002). Using the World Bank's international poverty standard of $1.00 per day, some estimates indicate that the number of rural poor in China has decreased from 260 million in 1990 to 106 million in 1998, or from one-third to less than one-tenth of the population (World Bank, 1997, 2000). Most of the decrease in hookworm among China's rural poor has taken place either in the eastern provinces or in the cities along its pacific rim. Cities such as Shanghai, Hangzhou, and Fuzhou have experienced unprecedented prosperity and annual economic growth rates of

7 to 8 percent. As a result, they rival Hong Kong as new centers of trade and commerce in Asia. A World Bank analysis suggests that rural poverty will continue to diminish along China's coast and eastern provinces, leaving much of the residual poverty to China's mountainous regions and the provinces of West China (World Bank). The depth of poverty in the western provinces is now more severe than the rest of China.

The eastern province of Jiangsu exemplifies how rural poverty reduction translates into reduced endemic hookworm. Since the middle 1990s, Jiangsu has benefited from spillover economic development that began in nearby Shanghai. In 1997, hookworm was found in 12.5 percent of a village population compared to almost double that rate almost ten years previously (Table 3). In contrast, the prevalence (and intensity) rates in the traditionally poor hookworm-endemic regions of West China, such as in Sichuan and Yunnan remained the same in 1997 and 1998, or even increased, since hookworm was examined there during the nationwide survey. Hainan also still suffers from high rates of endemic hookworm. Despite its extreme poverty, hookworm is not endemic in the Northwest (Qinghai, Xinjiang and Tibet) because its cold and dry conditions are unfavorable for parasite transmission.

Figure 6 shows that hookworm infection is strongly linked to the economic development of the region. The poorest provinces, as measured by per capita GDP, have the highest prevalence rates of hookworm. Although the relationship between hookworm and poverty is solid and substantive, it is not yet possible to ascertain whether poverty creates conditions that are favorable for hookworm transmission, as it almost certainly does, or whether hookworm itself also contributes to low human economic productivity. Without sufficient data it is not yet possible to prove that endemic hookworm not only functions as a marker for poverty, but that it also directly drags down economic growth.

In China, hookworm is now a showcase for a growing divide between the newer wealthy urban regions in the East and poor rural areas in the Southwest (Hotez, 2002). During the last decade China's urban-based development schemes have favored eastern urban industry and foreign investment over the promotion of western agriculture (World Bank). Hookworm can therefore be expected to remain endemic among the estimated 21 million rural poor who live in the western provinces of Sichuan, Yunnan, Guizhou, and Guangxi. These include ethnic minority groups that may account for large populations of the absolute poor who live in the region. Hookworm will also continue to occur among the residual 5.7 and 3.2 million who live in hookworm-endemic regions of central (including Hainan) and southeastern China, respectively (World Bank). Together these 29 million rural poor represent the Chinese population that will remain at the very highest risk from hookworm infection. Over the next decade, the extent of China's hookworm problem is anticipated to reflect a balance between the rapidly diminishing numbers of China's rural poor in the East, high rates of rural poverty in the West, and an expanding geriatric population in both regions. Graying populations living in Sichuan, Yunnan, Guizhou, Guangxi, and Hainan will suffer the most from endemic hookworm.

Therefore, in the long term, elimination of soil-transmitted helminth infections depends upon economic development with consequent improvements in water supplies, sanitation and health education. Intensive use of anthelmintics can bring about a rapid reduction in transmission, such as seen in Japan and South Korea. In the absence of mass chemotherapy programmes however, a sustained impact can occur only with the increasing levels of education and economic prosperity that accompany reduction in poverty.

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Table 1
Disease classification for Ascaris lumbricoides infection

Type A: Reversible growth faltering in children and / or reduced physical fitness in children and adults, which lasts for the duration of the infection. This denotes a deficit in health that is recovered completely once the individual loses the infection, or the worm burden drops below a certain threshold.

Type B: Permanent growth retardation, which is a lifelong consequence of infection, occurring only in children. This denotes a deficit that may be recovered, but only partially, even if the individual loses the infection completely.

Type C: Clinically overt, acute illness such as intermittent abdominal pain or discomfort, nausea, anorexia or diarrhoea, of short duration and mild to moderate severity. The severity of illness would be such that it causes the individual to seek medical attention.

Type D: Acute complications such as intestinal obstruction and its complications, biliary or pancreatic disease, appendicitis, peritonitis, etc. These are of sufficient severity for the affected individual to be hospitalized for some days.

(Adapted from de Silva et al, 1997b)

Table 2
Estimates of numbers infected with *Ascaris lumbricoides* and at risk of morbidity and mortality by age (from de Silva et al 1997b)

	Population (in millions)	Infections (in millions)	Nos. at risk of each type of morbidity (in thousands)				No. of deaths (in thousands)
Age group		*n* (%)	A	B	C	D	
0 –5	553	158 (28.6)	20 830	625	3940	78	3.9
5 – 10	482	167 (34.6)	18 880	566	5161	78	3.9
10 –15	437	154 (35.2)	11 181	335	2184	47	2.4
15+	2647	795 (30.0)	8151	0	238	5	0.3
Total	4120	1274	59 043	1527	11 523	209	10.5

Table 2
Estimates of numbers infected with *Ascaris lumbricoides* and at risk of morbidity and mortality by region (from de Silva et al 1997b)

	Population (in millions)	Infections (in millions)	Nos. at risk of each type of morbidity (in thousands)				No. of deaths (in thousands)
Region		*n* (%)	A	B	C	D	
SSA	510	105 (20.6)	3382	93	623	14	0.7
LAC	444	171 (38.5)	8783	230	1716	30	1.5
MEC	503	96 (19.1)	3229	87	622	13	0.6
IND	850	188 (22.1)	7218	190	1416	27	1.3
CHN	1134	410 (36.2)	18 080	439	3537	71	3.5
OAI	683	303 (44.4)	18 351	487	3609	55	2.8
Total	4120	1274	59 043	1527	11 523	209	10.5

Table 3
Prevalence of Human Hookworm Infection in Selected Provinces 1997-1998

Province	No. Patients	Prevalence	Age-Group Highest Prevalence	Reference
Anhui	488	33%	41-50 y.o.	Wang et al, 1999
Hainan	631	60%	>40 y.o.	Gandhi et al, 2001
Jiangsu	876	12%	>50 y.o.	Sun et al, 1998
Sichuan	520	67%	>65 y.o.	Liu et al, 1999
Yunnan	766	37%	>60 y.o.	Zhan et al, 2000

Table 4
Difference in prevalence of helminth infection between male and female school-children derived from published surveys in Africa and Asia.

Species / country	Comparisons	Mean difference (± S.D)	*P* value
A. lumbricoides	38	-0.09 (8.4)	0.946
T. trichiura	27	-1.46 (4.6)	0.099
Hookworm	77	-3.07 (9.1)	0.004
S. haematobium	220	-4.47 (11.6)	<0.001
S. mansoni	126	-4.25 (17.1)	0.006

Table 5
Difference in prevalence of helminth infection between male and female schoolchildren in different African countries. Schools with prevalences of 0% were excluded from the analysis.

Species / country	Comparisons	Mean difference (± S.D)	*P* value
A. lumbricoides			
Cameroon	209	-3.92 (14.4)	>0.001
Ghana	22	-1.46 (8.2)	0.412
Kenya	25	-0.46 (13.2)	0.862
Tanzania (coast)	32	-1.09 (13.8)	0.658
Tanzania (lake)	6	-0.48 (2.1)	0.589
Uganda	62	-0.33 (7.3)	0.727
Overall	**356**	**-2.58 (12.9)**	
T. trichiura			
Cameroon	232	-2.08 (12.7)	0.013
Ghana	14	-0.89 (3.6)	0.363
Kenya	25	-1.97 (12.6)	0.442
Tanzania (coast)	24	-1.85 (10.7)	0.405
Tanzania (lake)	9	0.15 (1.8)	0.804
Uganda	59	-0.19 (8.5)	0.858
Overall	**363**	**-1.65 (11.6)**	
Hookworm			
Cameroon	214	-4.58 (14.0)	>0.001
Chad	15	-4.13 (12.3)	0.314
Ghana	30	-15.07 (12.5)	>0.001
Kenya	25	-7.67 (11.2)	0.002
Tanzania (coast)	38	-4.14 (16.2)	0.125
Tanzania (lake)	59	-4.84 (10.6)	0.001
Uganda	166	-2.27 (12.2)	0.018
Overall	**547**	**-4.05 (13.0)**	
S. haematobium			
Cameroon	120	-7.14 (15.1)	>0.001
Chad	16	-11.07 (16.7)	0.018
Ghana	29	-0.22 (8.3)	0.989
Tanzania (coast)	38	-2.02 (18.2)	0.500
Tanzania (lake)	59	-10.72 (10.2)	>0.001
Overall	**262**	**-6.66 (14.5)**	
S. mansoni			
Cameroon	110	-3.37 (12.4)	0.005
Kenya	25	-2.00 (7.4)	0.190
Tanzania (lake)	59	-1.86 (6.2)	0.028
Uganda	104	-4.13 (11.8)	0.001
Overall	**300**	**-3.12**	

Figure 1
Prevalence and intensity of human Ascaris infection in Cameroon

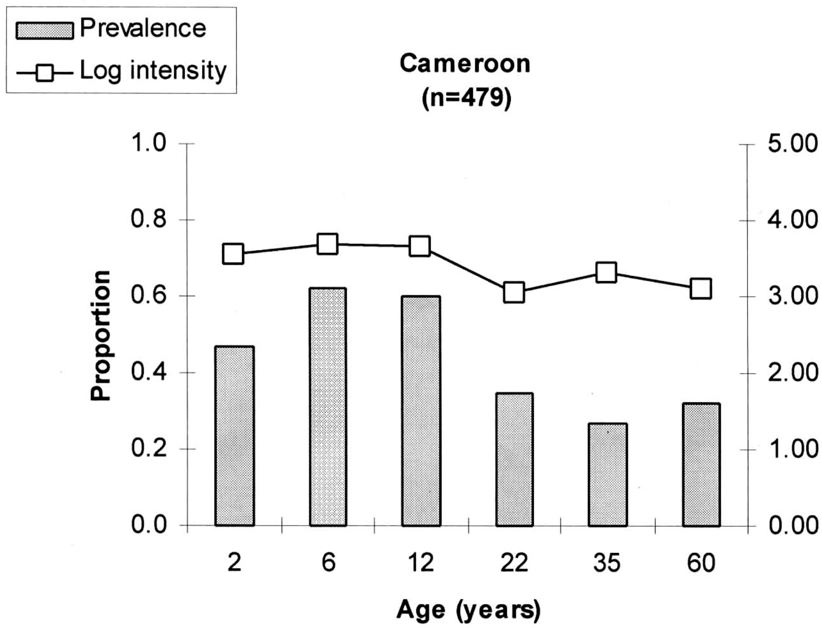


Figure 2
Prevalence and intensity of human Trichuris infection in Cameroon

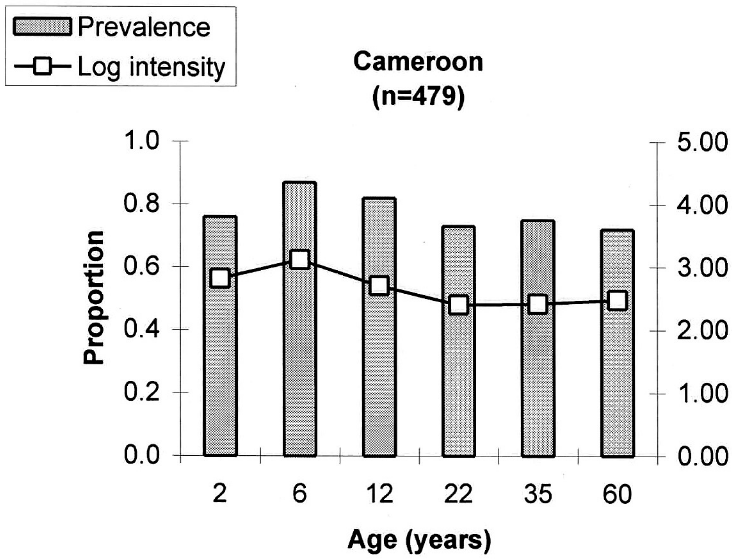
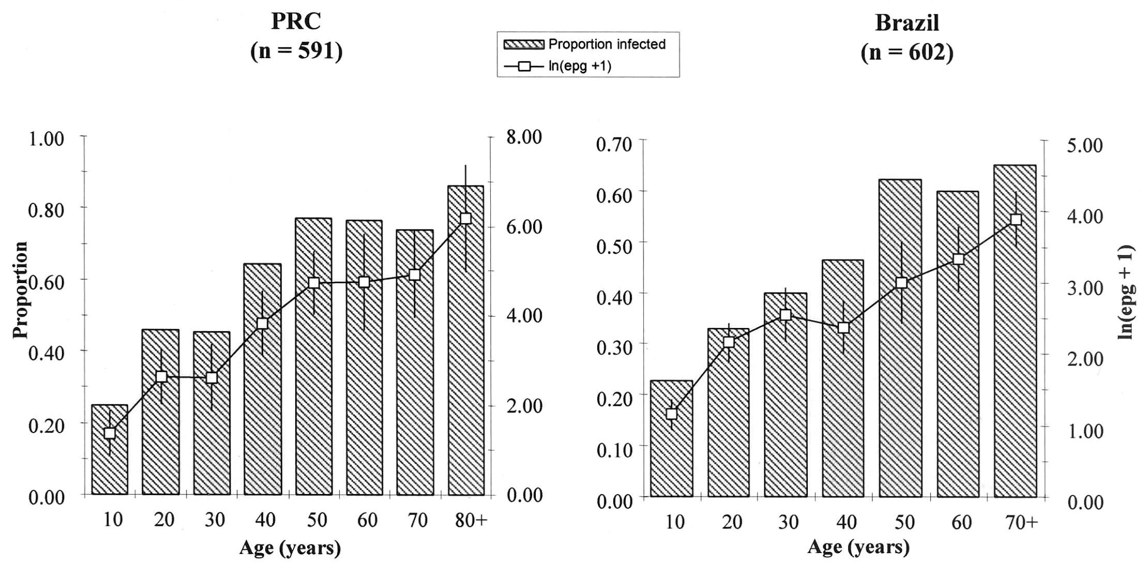
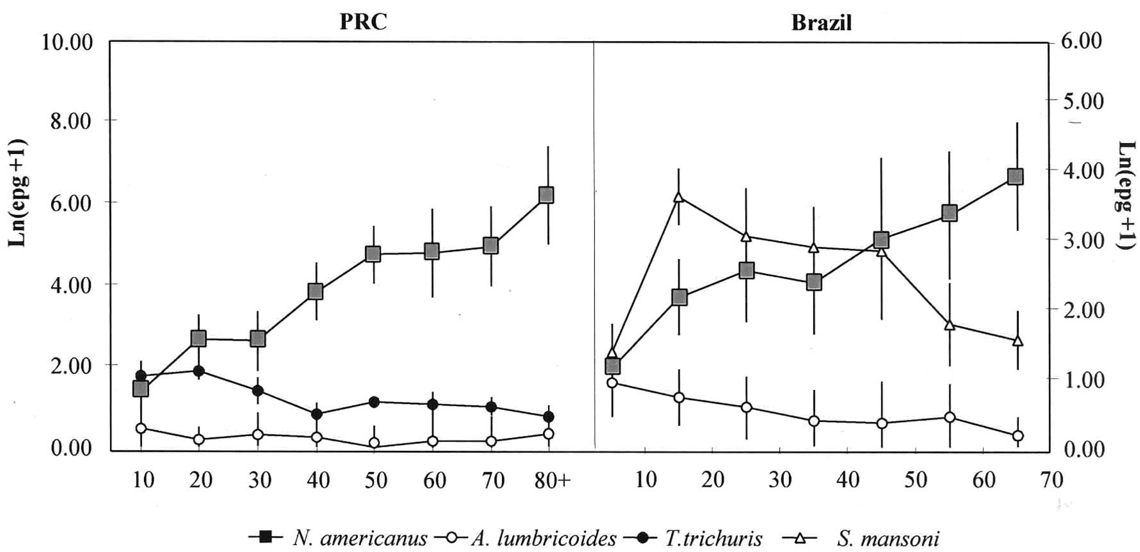


Figure 3



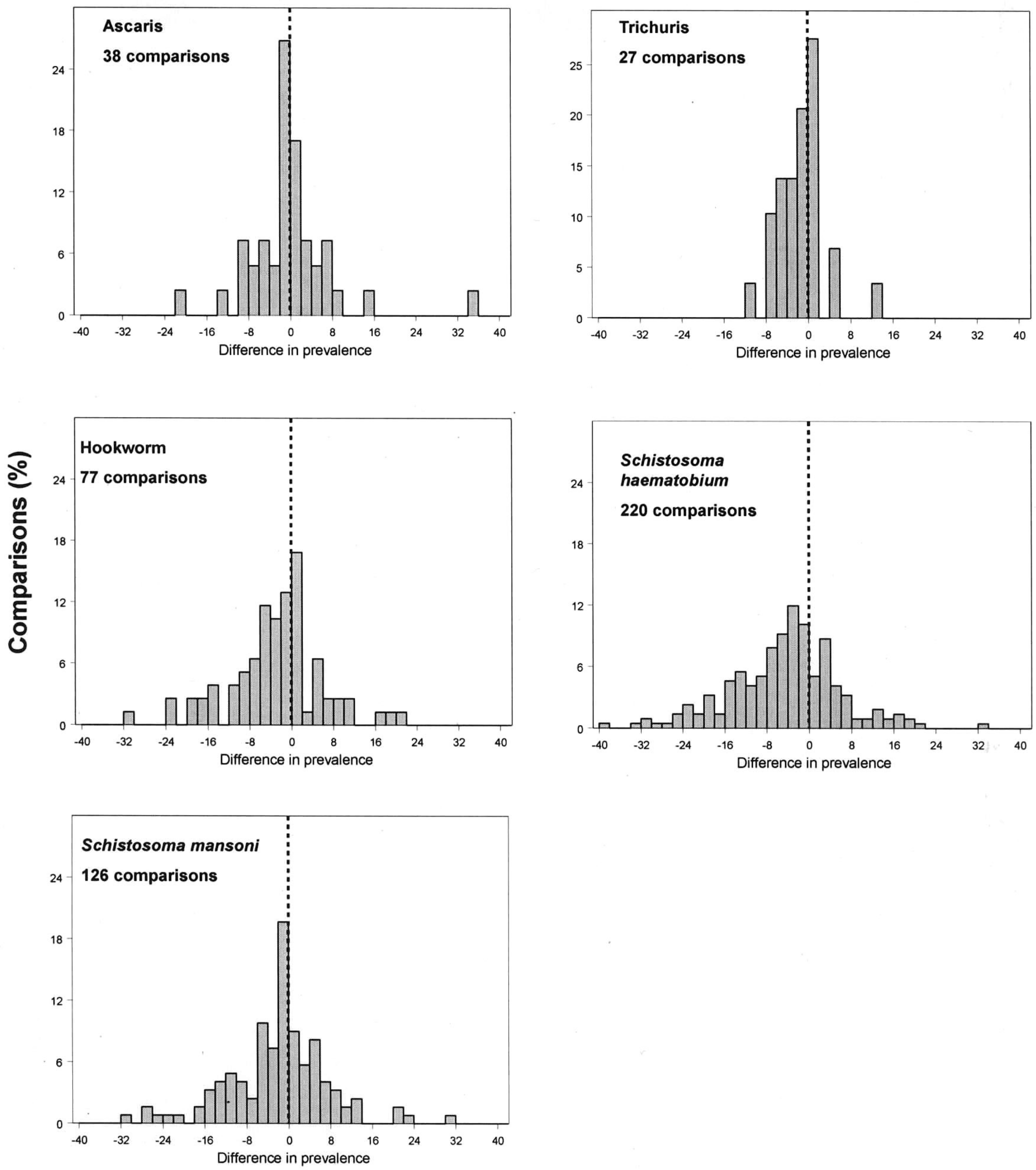
The prevalence and intensity of infection with *Necator americanus* increases with age in two endemic areas: Hainan Province, PRC (1999) and Minas Gerias, Brazil (2000). Data are from cross-sectional studies. Analysis of variance showed that egg counts were significantly different ($P < 0.001$) among the age intervals, and that the eldest 4 age intervals were significantly different ($P < 0.05$) from the younger age intervals, but not different from each other.

Figure 4



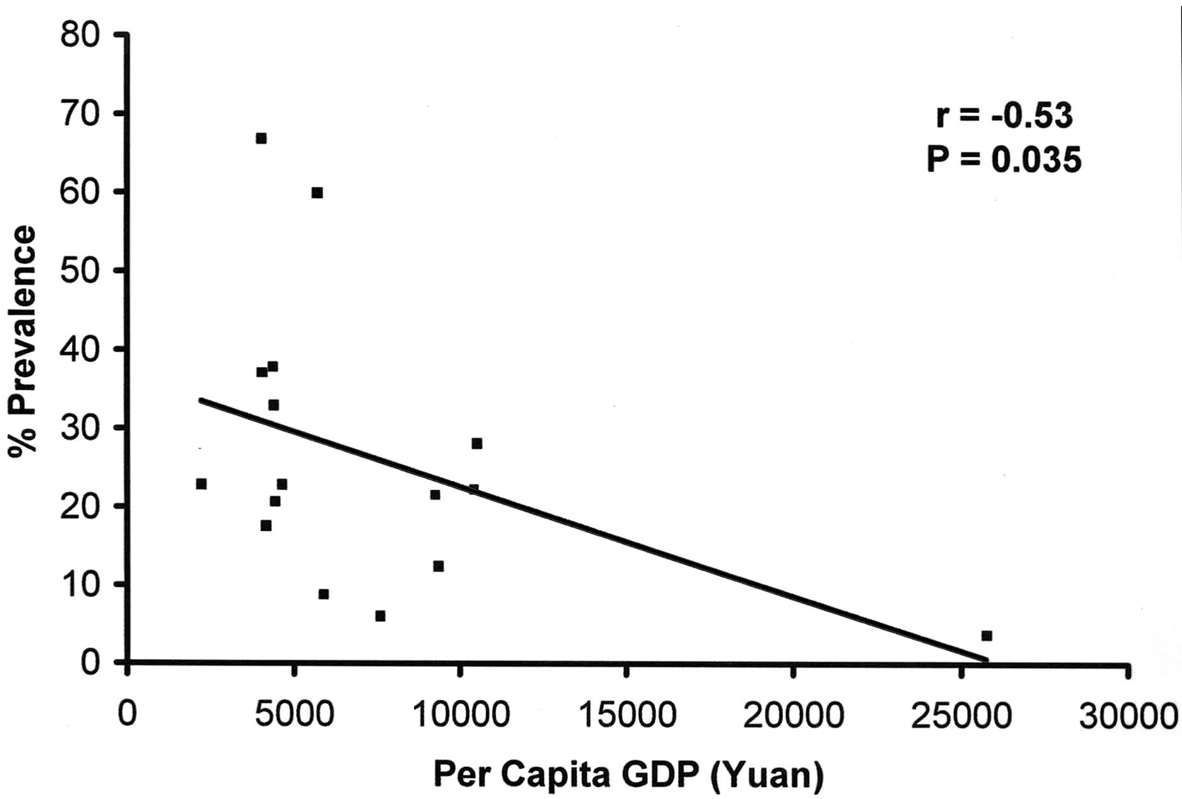
The age distribution of *N. americanus* differs from other STHs such as *A. lumbricoides, T. trichiura*, as well as *S. mansoni*. Panel A shows the relationship between age and infection intensity for three STHs in a cross–sectional study from Hainan, PRC. *A. lumbricoides* and *T. trichiura* peak epg among children and then decline into adulthood. The intensity of infection with N. americanus increases with age, peaking in eldest age category(80+). Panel B shows the distribution for *N. americanus* in relation to other helminth infections, Minas Gerais, Brazil. The distribution of *S. mansoni* infection intensity shows a traditional convex curve with age, increasing dramatically in young adults. The intensity of infection with *N. americanus* again increases steadily with age, peaking in the eldest age categories.

Figure 5



Frequency distribution of differences in the prevalence of infection between male and female schoolchildren for (a) *A. lumbricoides*, (b) *T. trichiura*, (c) hookworm, (d) *S. haematobium*, and (e) *S. mansoni*. Estimates based on published survey data. Values to the left of the line represent indicate higher prevalence in males, and values to the right indicate higher prevalence in females.

Figure 6
Hookworm prevalence in endemic regions of China as function of per capita GDP*



Reproduced from Hotez, 2002. Hookworm prevalence figures were obtained from the nationwide parasite survey completed in 1992,11 except for updated figures for Sichuan (Liu et al, 1999), Yunnan (Zhan et al, 2000), Jiangsu (Sun et al, 1998), and Anhui Provinces (Wang et al, 1999). Per capita GDP data were obtained from Benwick and Donald, 1999.

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